The American Journal of CARDIOLOGY

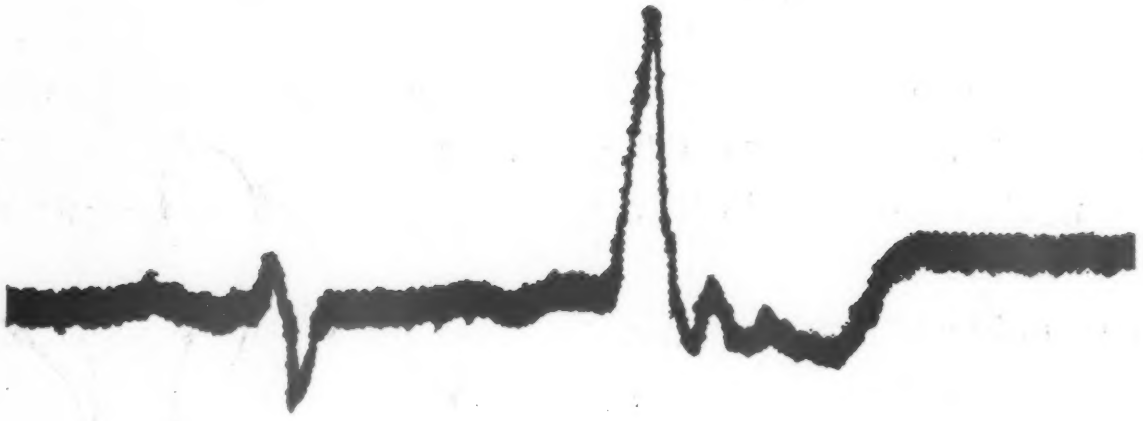
OFFICIAL JOURNAL OF THE *American College of Cardiology*

Symposium on Amine Oxidase Inhibitors

INDEX ISSUE

A PUBLICATION OF THE *Yorke* GROUP

DECEMBER 1960



for cardiac arrhythmias... obvious advantages

PRONESTYL® HYDROCHLORIDE

SQUIBB PROCAINE AMIDE HYDROCHLORIDE

Pronestyl offers obvious advantages over quinidine and procaine in the management of cardiac arrhythmias: "Procaine amide [Pronestyl] should be the drug of choice in arrhythmias of ventricular origin." [1]—on oral administration, side effects are less marked than with quinidine—administered I. V., Pronestyl is safer than a corresponding I.V. dose of quinidine—administered I. M., Pronestyl acts faster than I. M. quinidine[2]—Pronestyl sometimes stops arrhythmias which have not responded to quinidine[3,4]—Pronestyl may be used in patients sensitive to quinidine—more prolonged action, less toxicity, less hypotensive effect than procaine—no CNS stimulation such as procaine may produce.

Supply: For convenient oral administration: Capsules, 0.25 gm., in bottles of 100.
For I. M. and I. V. administration: Parenteral Solution, 100 mg. per cc., in vials of 10 cc.

References: 1. Zapata-Diaz, J., et al.: Am. Heart J. 43:854, 1952. 2. Modell, W.: In Drugs of Choice, C.V. Mosby Co., St. Louis, 1958, p. 454. 3. Kayden, H. J., et al.: Mod. Concepts Cardiovasc. Dis. 20:100. 1951. 4. Miller, H., et al.: J.A.M.A. 146:1004, 1951.

SQUIBB *Squibb Quality—the Priceless Ingredient*

HOW WOULD YOU DEFINE *the ideal diuretic?*

The qualities to be sought in an ideal diuretic have been listed[1] as follows:

"(1) Sustained rather than abrupt violent action.

(2) Reduced capacity for electrolyte upheaval.

(3) Convenience of administration; self-administration (oral, rectal, or subcutaneous).

(4) Decreased toxicity (systemic and local irritant action, especially of the gastrointestinal tract).

(5) Effectiveness where others are ineffectual or contra-indicated.

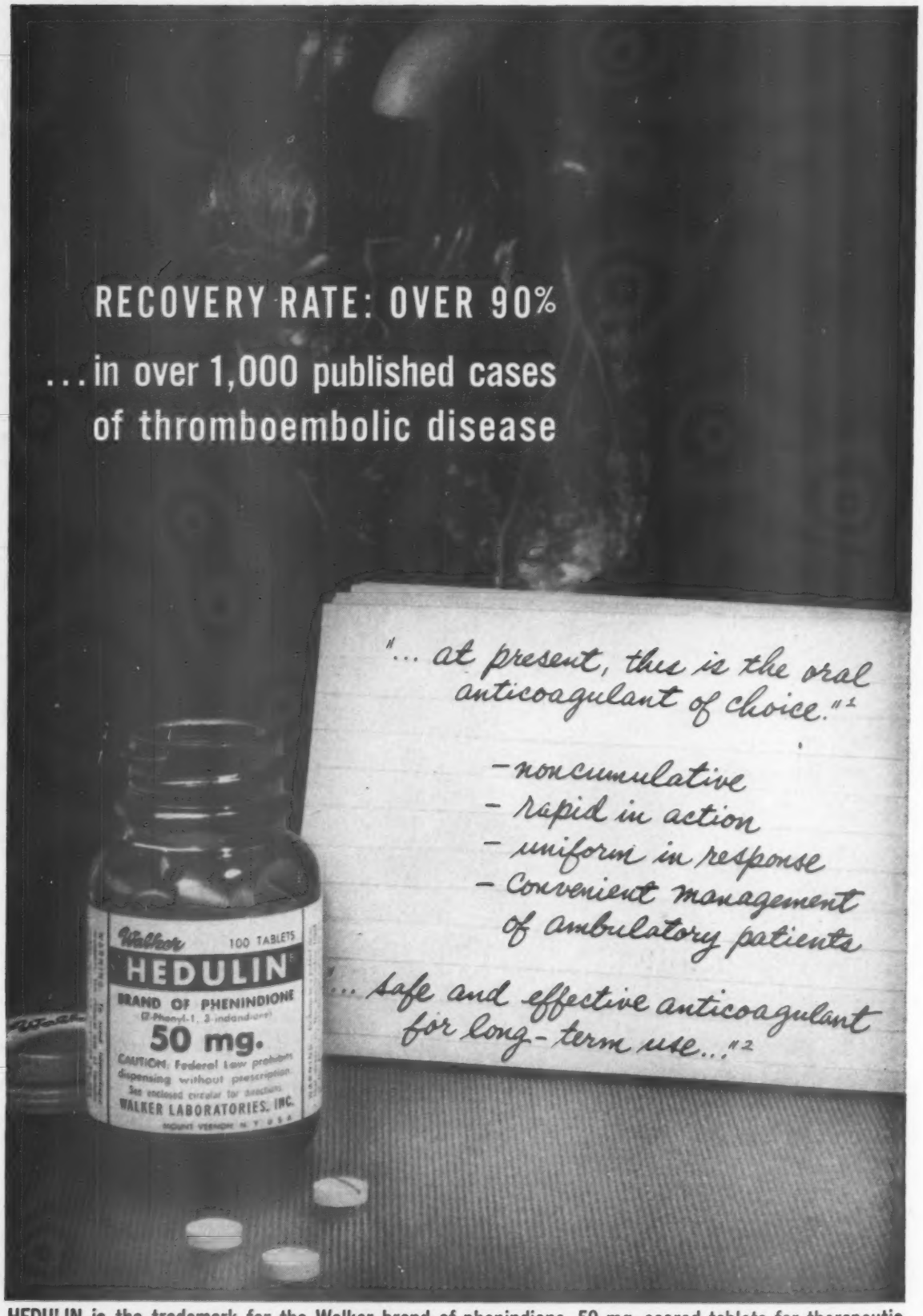
(6) Applicability in cases with a history of allergic reaction to other diuretics."

It would be rash to term any drug ideal. It is safe to say, however, that Aldactone very closely approximates these six requirements. Most importantly, Aldactone often relieves edema and ascites resistant or not optimally responsive to conventional diuretics. By blocking the *action* of the potent salt-retaining hormone, aldosterone, Aldactone, used alone or in synergistic combination with other potent agents, establishes satisfactory diuresis in most edematous patients who have heretofore been considered beyond the help of medical management. Aldactone offers a fundamentally new approach to the control of edema in such disorders as congestive heart failure, hepatic cirrhosis, the nephrotic syndrome and idiopathic edema.

ALDACTONE® is supplied as compression-coated yellow tablets of 100 mg.
(brand of spironolactone)

1. Modell, W.: Am. J. Cardiol. *3*:139 (Feb.) 1959.

Research in the Service of Medicine G. D. SEARLE & CO.



HEDULIN is the trademark for the Walker brand of phenindione. 50 mg. scored tablets for therapeutic use; 20 mg. scored tablets for prophylactic use. Bottles of 100 and 1,000. For more detailed information and a clinical trial supply of Hedulin, write to Walker Laboratories, Inc., Mount Vernon, N. Y.

1. Breneman, G. M., and Priest, E. McC.: Am. Heart J. 50:129 (July) 1955. 2. Tandowsky, R. M.: Am. J. Cardiol. 3:551 (April) 1959.

Symbol of Distinguished Journalism

The American Journal of Cardiology

THE AMERICAN JOURNAL OF CARDIOLOGY is published monthly by The American Journal of Medicine, Inc., Executive and Editorial Offices, 11 East 36th Street, New York 16, N. Y. December 1960, Volume 6, No. 6. Publication Office, 20th and Northampton Streets, Easton, Pa. Second-class postage paid at Easton, Pa. Official Journal of the American College of Cardiology.

SUBSCRIPTIONS: United States $12.00 a year; Canada $13.00; Foreign $15.00
SINGLE COPIES: Regular Issues $2.00; Symposium and Special Issues $4.00

MAIL CHANGES OF ADDRESS AND SUBSCRIPTION ORDERS TO: The American Journal of Cardiology, 11 East 36th Street, New York 16, N. Y. Change of address must reach us one month in advance.

MANUSCRIPTS: All manuscripts should be typewritten double space and submitted in duplicate to the Editorial Office of The American Journal of Cardiology, 11 East 36th Street, New York 16, N. Y. The top should be indicated on the back of each photograph. Reference style: Smith, J. S. Treatment of cardiac failure. *Am. J. Cardiol.*, 3: 274, 1959.

AMERICAN COLLEGE OF CARDIOLOGY: All communications for the College should be addressed to the American College of Cardiology, Office of the Executive Director, 350 Fifth Ave., New York 1, N. Y.

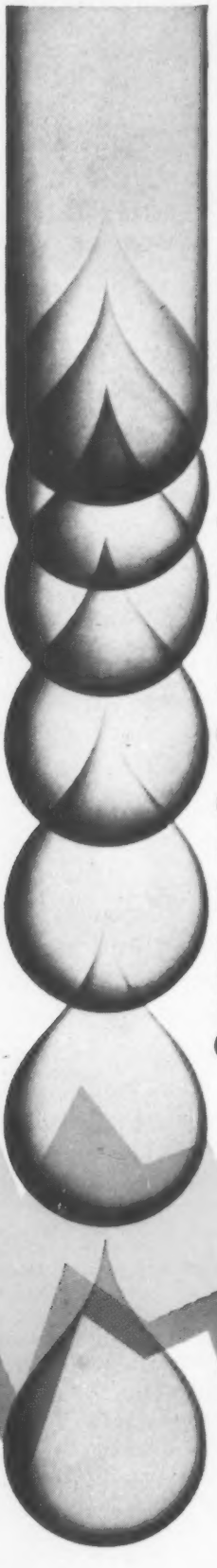
PLINY A. PORTER—Publisher
JOHN J. MARTIN—Assistant Publisher

New Hygroton® Geigy

brand of chlorthalidone

longest in action... smoothest in effect

in hypertension and edema



greater loss of sodium
lesser loss of potassium

A new antihypertensive-saluretic, Hygroton, now enables still more effective control of hypertension and edema.

more evenly sustained therapeutic response
Because it is more prolonged in action than any other diuretic,[1] Hygroton affords a smoother, more evenly sustained response.

more nearly pure natriuretic effect
Hygroton produces only minimal potassium loss . . . affords a better sodium-potassium ratio than other saluretics.[3]

more liberal diet for the patient
As a rule, with Hygroton, restriction of dietary salt is unnecessary.

more convenience and economy
For maintenance therapy three doses per week suffice to manage the vast majority of cases.[2]

in arterial hypertension
Sustained control without side reactions.

in edematous states
Copious diuresis without electrolyte imbalance.

Hygroton®, brand of chlorthalidone: White, single-scored tablets of 100 mg. in bottles of 100.

References:
(1) Stenger, E. G., et al.: Schweiz. med. Wchnschr. 89:1126, 1959. (2) Fuchs, M., Res: et al.: Current Therap. Research 2:11, January, 1960. (3) Ford, R. V.: Manuscript submitted for publication.

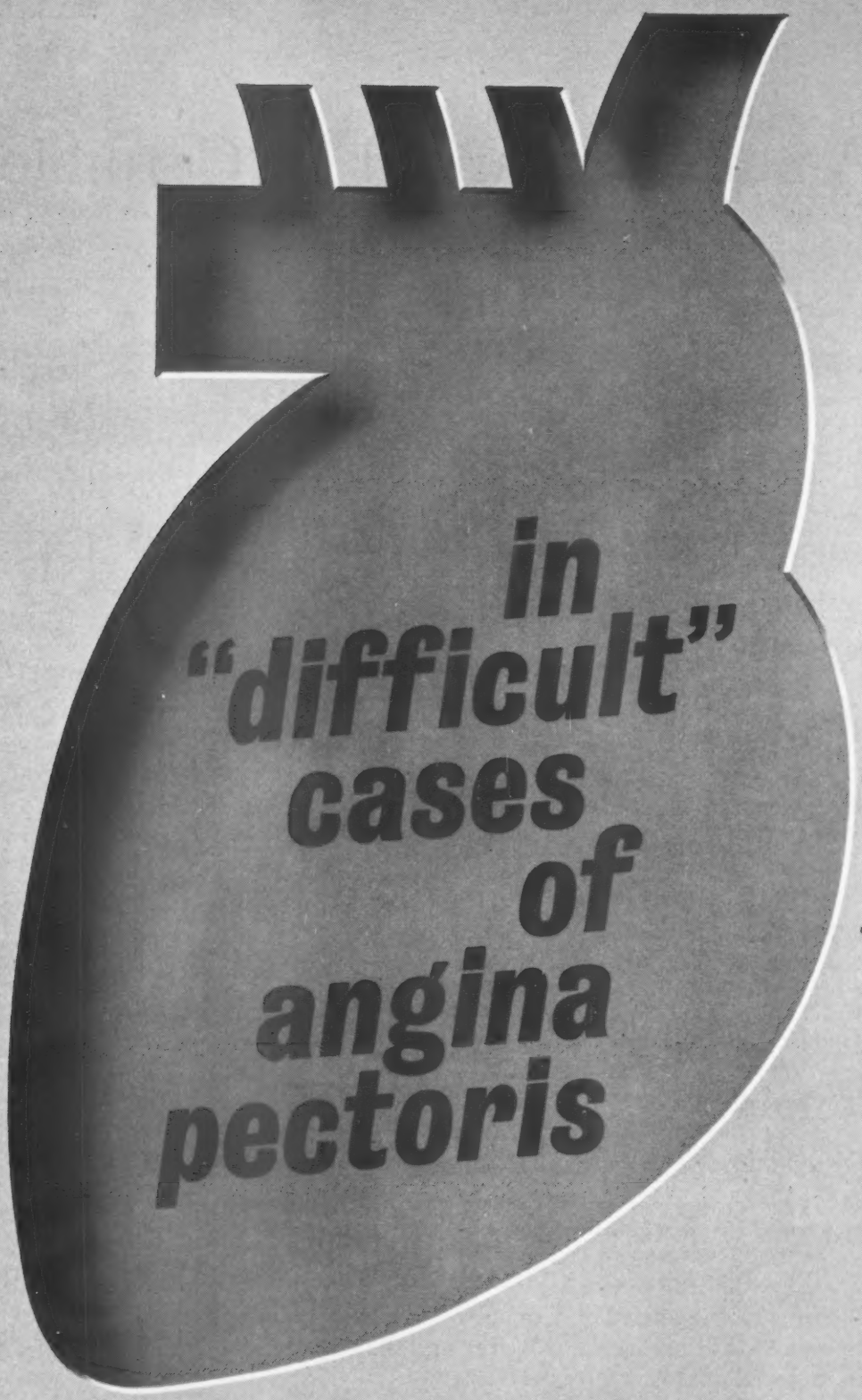
Geigy, Ardsley, New York HY 234-60

The American Journal of Cardiology

Volume VI DECEMBER 1960 Number 6

CONTENTS

Contents continued on page 7



Marplan

prevents anginal pain[1-4]
increases exercise tolerance[2,5,6]
reduces nitroglycerin requirements[2,3]

A potent regulator of amine oxidase, Marplan has demonstrated a high degree of effectiveness in moderately severe to intractable angina pectoris. Improvement on Marplan ranged from a reduction in the number of attacks to virtual abolition of the anginal state. With Marplan, anginal relief is enhanced by a more confident mental climate – improving the chances of success of the entire prophylactic regimen. However, since the precise manner in which Marplan improves the cardiac status is as yet undefined, it is imperative that patients be instructed to maintain the same restrictions of activity in force prior to Marplan therapy. Consult literature and dosage information, available on request, before prescribing.

References: 1. W. Hollander and R. W. Wilkins, in J. H. Moyer, Ed., Hypertension, Philadelphia, W. B. Saunders Co., 1959, p. 399. 2. R. W. Obiath, paper read at American Therapeutic Society, 60th Annual Meeting, Atlantic City, N. J., June 6, 1959. 3. N. Bloom, Virginia M. Month., 87:23, 1960. 4. T. Winsor and P. Zarco, Angiology, 11: (Part 2), 67, 1960. 5. G. C. Griffith, Clin. Med., 6:1555, 1959. 6. G. C. Griffith, Dis. Nerv. System, 21 (Suppl.), 101, 1960.

MARPLAN® – 1-benzyl-2-(5-methyl-3-isoxazolylcarbonyl) hydrazine

ROCHE
ROCHE
LABORATORIES
Division of Hoffmann-La Roche Inc.

Experimental Study

New Methods

Contents continued on page 9

New Alvodine ethanesulfonate

trademark

Brand of piminodine ethanesulfonate

Analgesic potency as great as morphine without drowsiness or hypnosis*

Alvodine, a new and powerful narcotic analgesic, relieves pain as effectively as morphine, yet is much safer because it is free from the high incidence and severity of morphine's side effects. Alvodine is effective *orally* as well as parenterally. Alvodine causes almost no sedation, drowsiness or euphoria. Respiratory and circulatory depression are rare with customary doses; nausea and vomiting are uncommon. Constipation has not been reported.

Preferred agent for specific situations

Alvodine is especially well suited for *postoperative analgesia* because it permits most patients to remain alert and at the same time free from pain. The risk of postoperative pulmonary hypostasis and venous stagnation is decreased because the use of Alvodine allows patients to be mobilized sooner.

Alvodine is ideal for *ambulatory* and *semiambulatory patients* who are in need of strong analgesia. Patients with cancer remain alert and can often carry on their normal daily activities when freed of pain by *oral* doses of Alvodine.

Dosage: Orally, from 25 to 50 mg. every four to six hours as required. By subcutaneous or intramuscular injection, from 10 to 20 mg. every four hours as required.

How Supplied: Alvodine tablets, 50 mg., scored. Alvodine ampuls, 1 cc., containing 20 mg. per cc. *Narcotic Blank Required.*

Winthrop LABORATORIES
New York 18, N. Y.

Write for Alvodine brochure containing detailed information on clinical experience, addiction liability, side effects and precautions.

*In more than 90% of patients.

CONTENTS continued—December 1960

VOLUME SIX NUMBER SIX

Review

Report on Therapy

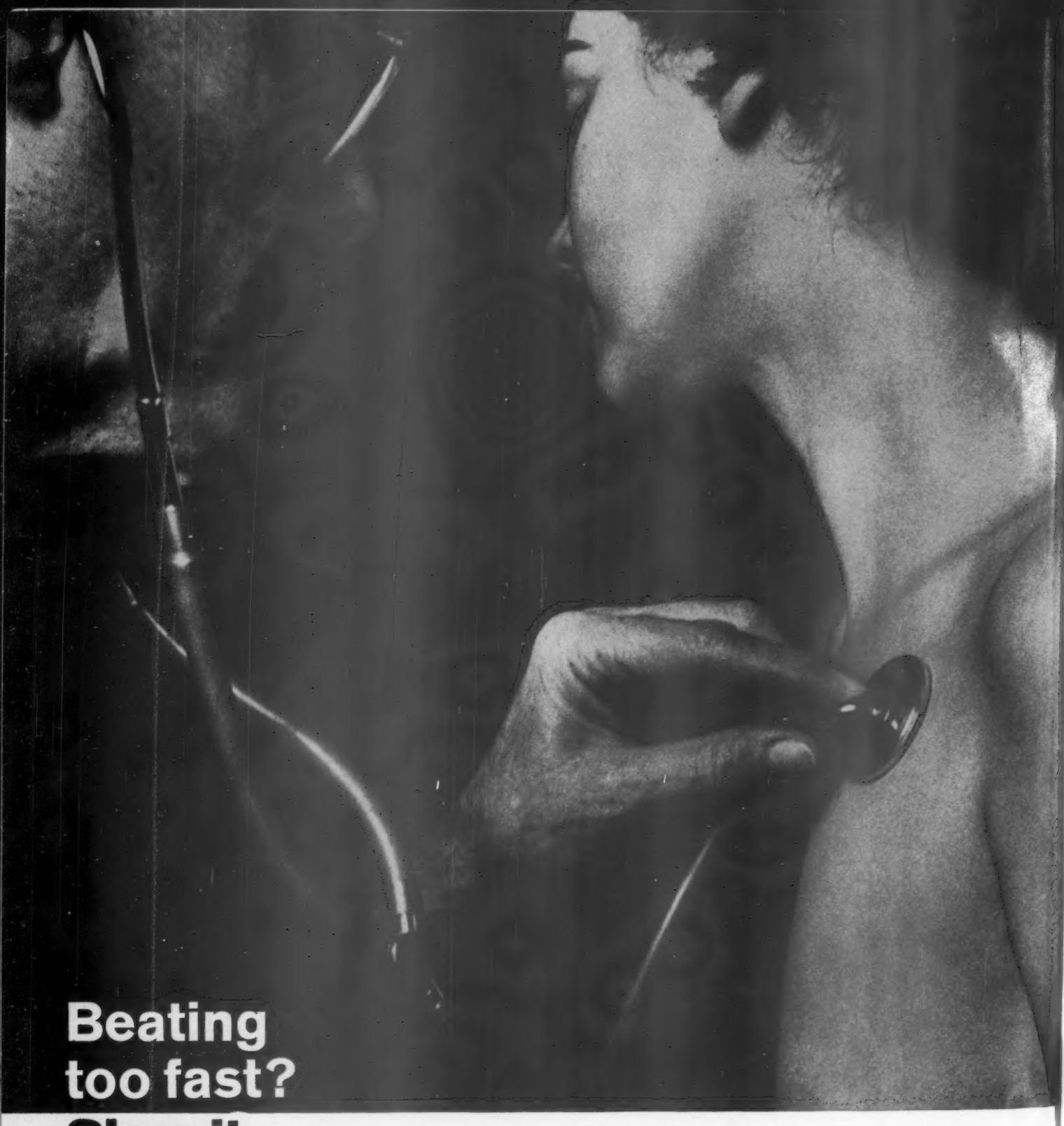
Historical Milestones

Case Report

Diagnostic Shelf

Symposium on Amine Oxidase Inhibitors

Contents continued on page 11



Beating too fast? Slow it down with SERPASIL®

(reserpine CIBA)

Serpasil has proved effective as a heart-slowing agent in the following conditions: mitral disease; myocardial infarction; cardiac arrhythmias; neurocirculatory asthenia; thyroid toxicosis; excitement and effort syndromes; cardiac neurosis; congestive failure. Serpasil should be used with caution in patients receiving digitalis and quinidine. It is not indicated in cases of aortic insufficiency.

SUPPLIED: Tablets, 0.1 mg., 0.25 mg. (scored) and 1 mg. (scored). Complete information available on request.

CIBA
SUMMIT • NEW JERSEY

8/2810MB

CONTENTS continued—December 1960

VOLUME SIX NUMBER SIX

Contents continued on page 13

Special Departments

Index to Advertisers on page 58

14 NEW BOOKS IN CARDIOLOGY

☐ **THE EXERCISE ELECTROCARDIOGRAM IN OFFICE PRACTICE** *by E. Grey Dimond.* Pub. Jan. '61

☐ **CLINICS IN ELECTROCARDIOGRAPHY** *by Dale Groom.* Pub. Oct. '60, 160 pp., 398 il., $8.00

☐ **CHEMISTRY OF HEART FAILURE** *by William C. Holland and Richard L. Klein.* Pub. Aug. '60, 132 pp., 24 il. (Amer. Lec. Living Chemistry), $5.50

☐ **HEMOGLOBIN AND ITS ABNORMALITIES** *by Vernon M. Ingram.* Pub. Jan. '61, 176 pp., 93 il. (Amer. Lec. Living Chemistry)

☐ **CHEMISTRY AND THERAPY OF CHRONIC CARDIOVASCULAR DISEASE** *by Richard J. Jones and Louis Cohen.* Pub. Feb. '61 (Amer. Lec. Living Chemistry)

☐ **FETAL ELECTROCARDIOGRAPHY** *by S. D. Larks.* Pub. Dec. '60, about 133 pp., 70 il. (Amer. Lec. Gynecology and Obstetrics)

☐ **CHEMOTHERAPY OF HYPERTENSION** *by Sir George Pickering.* Pub. March '61, (Amer. Lec. Living Chemistry)

☐ **EMBOLIC DISPERSOIDS IN HEALTH AND DISEASE** *by Gus Schreiber.* Pub. Sept. '60, 104 pp., 12 il. (Amer. Lec. Living Chemistry), $5.50

☐ **AN OUTLINE GUIDE FOR THE CARE OF POST-OPERATIVE CARDIAC PATIENTS** *by Merle E. White.* Pub. Jan. '61

☐ **TOWARDS THE DIAGNOSIS OF CONGENITAL HEART DISEASE** *by W. Carleton Whiteside.* Pub. Oct. '60, 100 pp., $4.50

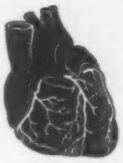
☐ **THE METABOLISM OF CARDIAC GLYCOSIDES:** A Review of the Absorption, Metabolism and Excretion of Clinically Important Cardiac Glycosides *by S. E. Wright.* Pub. March '60, 94 pp., 14 il. (Amer. Lec. Biochemistry and Biophysics), $4.75

☐ **CARDIACS AND DIABETICS IN INDUSTRY:** A Study in Work Experience *by Grace Wyshak, Leonid S. Snegireff and Augusta F. Law.* Pub. Feb. '61

☐ **QUANTITATIVE CELLULAR HEMATOLOGY** *by J. M. Yoffey.* Pub Oct. '60, 144 pp., 17 il. (2 in full color), (Amer. Lec. Hematology)

☐ **FUNCTIONAL BEHAVIOR OF THE MICROCIRCULATION** *by Benjamin W. Zweifach.* Pub. Feb. '61

CHARLES C THOMAS • PUBLISHER 301-327 East Lawrence Avenue **SPRINGFIELD • ILLINOIS**



in coronary insufficiency

Metamine® Sustained* helps you dilate the coronaries

METAMINE SUSTAINED (triethanolamine trinitrate biphosphate, 10 mg., in a unique sustained-release tablet) is a potent and exceptionally well tolerated coronary vasodilator. Pharmacological studies at McGill University demonstrated that METAMINE "exerts a more prolonged and as good, if not slightly better coronary vasodilator action than nitroglycerin . . ."[1] Work at the Pasteur Institute established that METAMINE exerts considerably less depressor effect than does nitroglycerin.[2] Virtually free from nitrate side effects (nausea, headache, hypotension), METAMINE SUSTAINED protects many patients refractory to other cardiac nitrates,[3] and, given b.i.d., is ideal medication for the patient with coronary insufficiency. Bottles of 50 and 500 tablets. Also: METAMINE, METAMINE WITH BUTABARBITAL, METAMINE WITH BUTABARBITAL SUSTAINED, METAMINE SUSTAINED WITH RESERPINE.

1. Melville, K. I., and Lu, F.C.: Canadian M.A.J., *65*:11, 1951. 2. Bovet, D., and Nitti-Bovet, F.: Arch. Internat. de pharmacodyn. et therap., *83*:367, 1946. 3. Fuller, H. L., and Kassel, L.E.: Antibiotic Med. & Clin. Therapy, *3*:322, 1956.

Thos. Leeming & Co. Inc. New York 17, N. Y.

*Patent applied for

In over five years

Proven

in more than
750 published clinical studies

Effective

FOR RELIEF OF ANXIETY
AND TENSION

Outstandingly Safe

For your reference: controlled studies on Miltown...

1. Blumberg, N. *et al.*: Fed. Proc. 17:351, March 1958. **2.** Boyd, L. J. *et al.*: Am. J. Cardiol. 3:229, Feb. 1959. **3.** Brick, H. *et al.*: J. Social Therapy 4:190, 1958. **4.** Bulla, J. D. *et al.*: Am. Pract. & Digest Treat. 10:1961, Nov. 1959. **5.** Ewing, J. A. and Haizlip, T. M.: Am. J. Psychiat. 114:835, March 1958. **6.** Friedman, A. P.: Ann. N. Y. Acad. Sc. 67:822, May 9, 1957. **7.** Greenberg, L. A. *et al.*: Ann. N. Y. Acad. Sc. 67:816, May 9, 1957. **8.** Holliday, A. R.: Northwest Med. 58:837, June 1959. **9.** Hollister, L. E. *et al.*: Dis. Nerv. System 17:289, Sept. 1956. **10.** Laird, D. M. *et al.*: Dis Nerv. System 18:346, Sept. 1957.

CM-2538

# of clinical use...

1 simple dosage schedule produces rapid, reliable tranquilization without unpredictable excitation

2 no cumulative effects, thus no need for difficult dosage readjustments

3 does not produce ataxia, change in appetite or libido

4 does not produce depression, Parkinson-like symptoms, jaundice or agranulocytosis

5 does not impair mental efficiency or normal behavior

Usual dosage: One or two 400 mg. tablets t.i.d.
Supplied: 400 mg. scored tablets, 200 mg. sugar-coated tablets. Also as MEPROTABS®—400 mg. *unmarked,* coated tablets; and as MEPROSPAN®—400 mg. and 200 mg. *continuous release* capsules.

®TRADE-MARK

.....[double-blind]

11. Lasagna, L.: J. Chron. Dis. 3:122, Feb. 1956. 12. Muhlfelder, W. J. *et al.*: Dis. Nerv. System 20:587, Dec. 1959. 13. Pollak, M.: Practitioner 184:231, Feb. 1960. 14. Rickels, K. *et al.*: J.A.M.A. 171:1649, Nov. 21, 1959. 15. Russek, H. I.: Am. J. Cardiol. 3:547, April 1959. 16. Tucker, K. and Wilensky, H.: Am. J. Psychiat. 113:698, Feb. 1957.

Miltown®

meprobamate (Wallace)

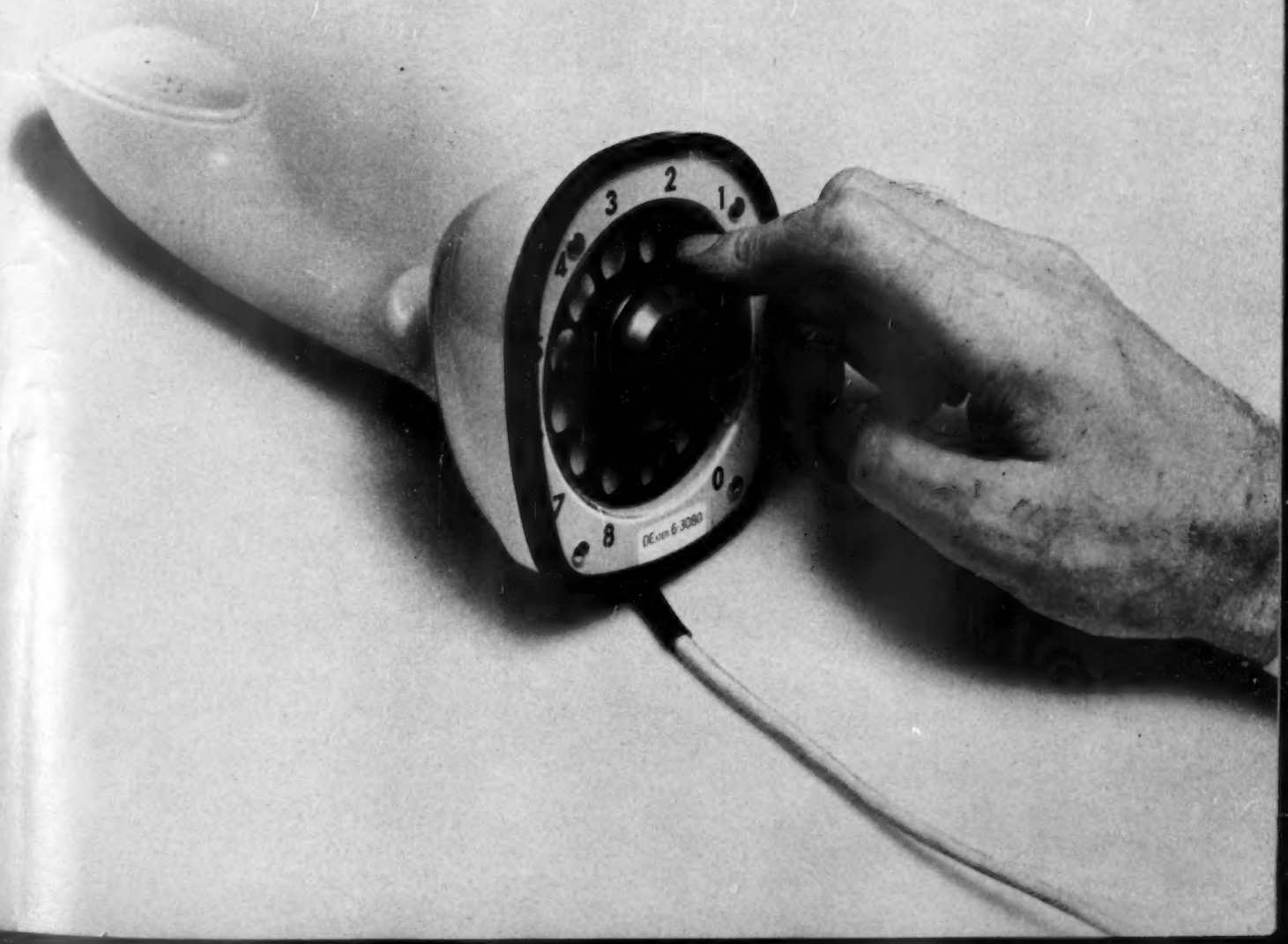
WALLACE LABORATORIES / *Cranbury, N. J.*

News from Abbott of a
truly practical "once a day"
diuretic-antihypertensive

ENDURON™

(METHYCLOTHIAZIDE, ABBOTT)

Longest acting of any available thiazide,
more sodium excretion with less potassium loss



Introducing **ENDURON**™

(METHYCLOTHIAZIDE, ABBOTT)

an improved way to treat edema and hypertension

once a day, every day

If you've found the thiazide diuretics helpful, you'll particularly appreciate Enduron. It provides the familiar benefits of oral thiazide therapy, but in a new and (we feel) more practical manner. ■ Dosage, for example, is engineered for the most practical schedule of all: "Once a day, every day." Easy to remember, easy to stick to. ■ More important, *duration* of action of this single daily dose is over 24 full hours. This means your first dose is still producing good diuresis or hypotensive action right up to the time when the next day's dose takes effect. ■ A single dose of 10 mg. produces a peak natruretic effect. By this we mean that the maximum possible effect occurs with 10 mg., and greater doses do not produce greater natruresis. However, most patients require just 5 mg. daily for satisfactory response. Some can be maintained on as little as 2½ mg. Such small doses afford a very safe therapeutic ratio. ■ If you're concerned about potassium, too, you'll like Enduron. It produces the least potassium excretion of any available thiazide. Depletion seldom becomes a factor in your therapy.

See next page for more details . . .

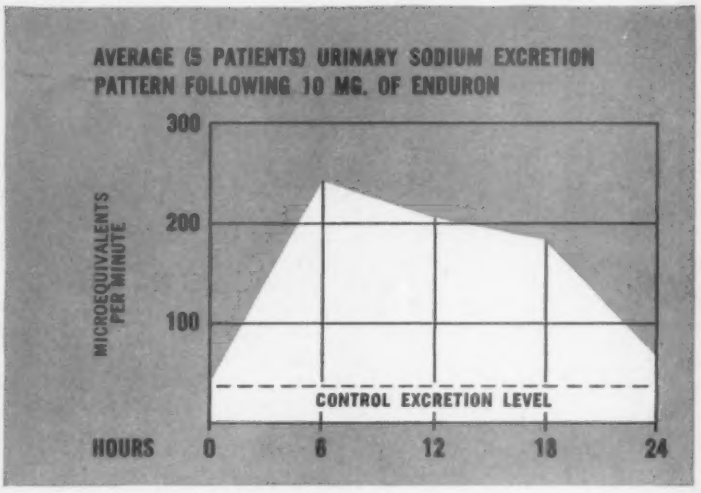
ENDURON™

(METHYCLOTHIAZIDE, ABBOTT)

logical culmination to thiazide therapy

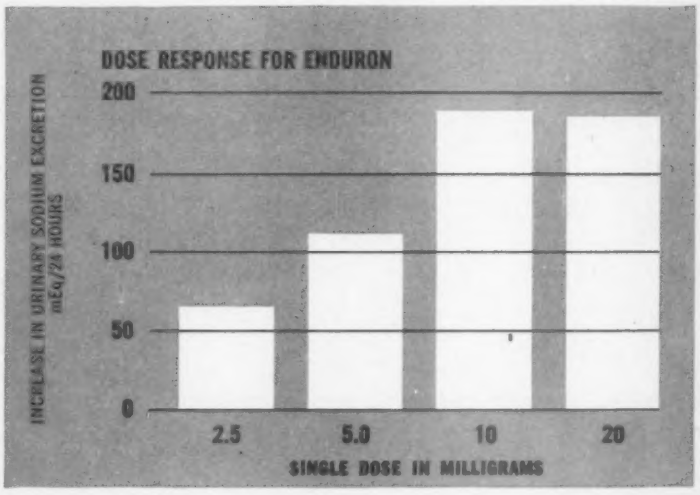
MOST SUSTAINED ACTION OF ANY AVAILABLE THIAZIDE

For once a day dosage to be really satisfactory, it must continue to produce therapeutic effect more than 24 hours later. Otherwise you can expect a gap in action until next day's dose has time enough to re-establish the effect. This gap is avoided with Enduron therapy. Its action remains well above control (i.e., undosed) levels, even at the end of the 24-hour period.



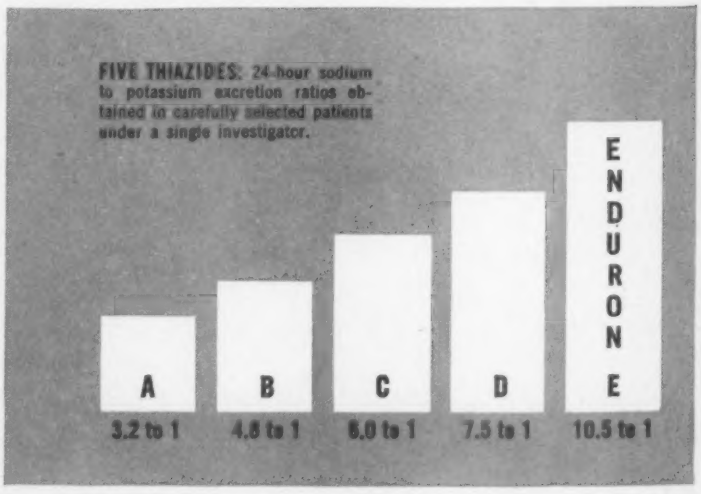
ACHIEVES PEAK NATRURESIS WITH JUST 10 MG.

Enduron is about 20 times more potent than hydrochlorothiazide by weight. It is also more potent compared at peak doses. As explained before, by peak doses we mean the smallest amounts which produce maximum natruretic response. In Enduron that peak is achieved with just 10 mg. (see graph). Larger doses than 10 mg. don't produce additional effect, and aren't needed.



MOST POTASSIUM-SPARING OF ANY AVAILABLE THIAZIDE

Enduron enhances sodium excretion, but doesn't boost potassium outgo proportionately. Its ratio of sodium excretion versus potassium is the most favorable of any available thiazide. In other words, Enduron leads to greater sodium excretion per unit of potassium excreted, and to less total potassium loss than other thiazides. Thus potassium depletion is rarely a problem.

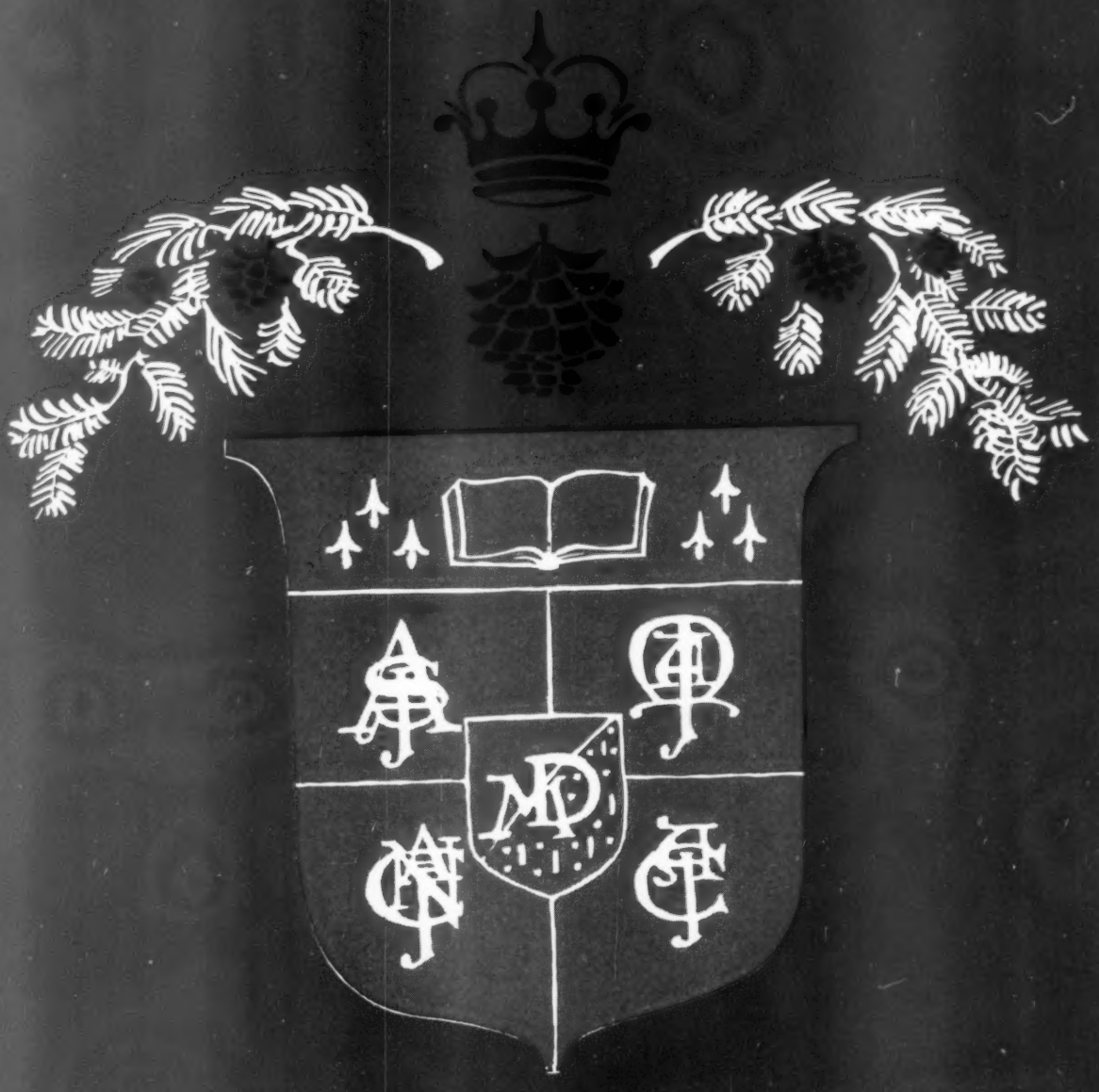


Enduron indications and side reactions are generally comparable to those for the earlier thiazides. Diuresis is prompt, but like other thiazides, several weeks may be required for full hypotensive effect. Enduron has a potentiating action, and you may wish to adjust dosage of other antihypertensive agents if they are used at the same time. Our literature gives full details; ask any Abbott representative or write Abbott Professional Services, North Chicago, Illinois.

Supplied in 2½-mg. (No. 6827) and 5-mg. (No. 6812) square tablets, bottles of 100 and 1000.

ABBOTT

011291



Season's Greetings

The American Journal of Surgery

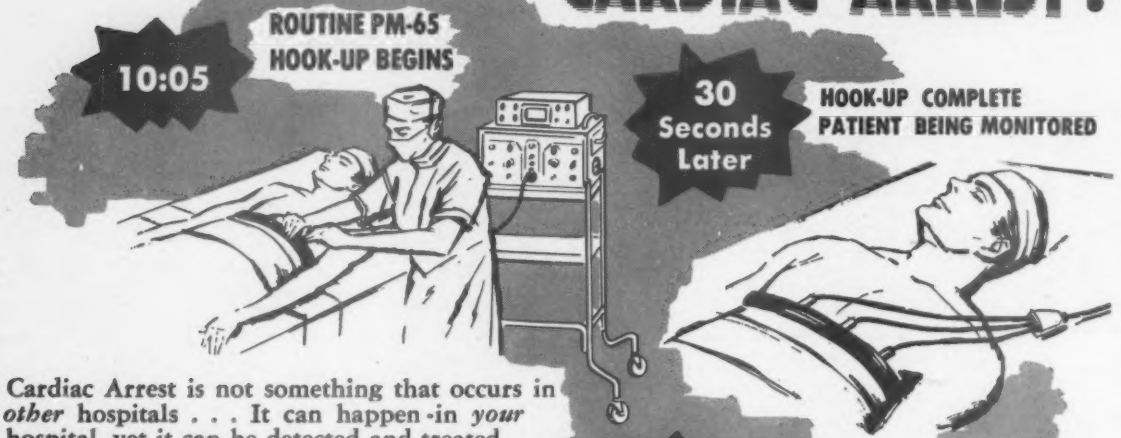
The American Journal of Medicine

The American Journal of Cardiology

The American Journal of Clinical Nutrition

Modern Drugs and Modern Drug Encyclopedia

Is this the way YOUR HOSPITAL detects and treats CARDIAC ARREST?



Cardiac Arrest is not something that occurs in *other* hospitals . . . It can happen in *your* hospital, yet it can be detected and treated successfully.

Illustrated is the method used by an ever-increasing number of hospitals to combat the dreaded occurance of Cardiac Arrest.

Electrodyne, working in close cooperation with leading heart specialists, has developed a complete line of proven instruments for the preventive detection and automatic treatment of Cardiac Arrest.

During Thoracic Surgery the same electrodes may be hooked to the extremities. Provision for direct stimulation of the heart available.

Electrodyne PM-65 with (optional) Electrocardioscope, for the detection and treatment of Cardiac Arrest. For detailed information on this and other Electrodyne equipment, write:

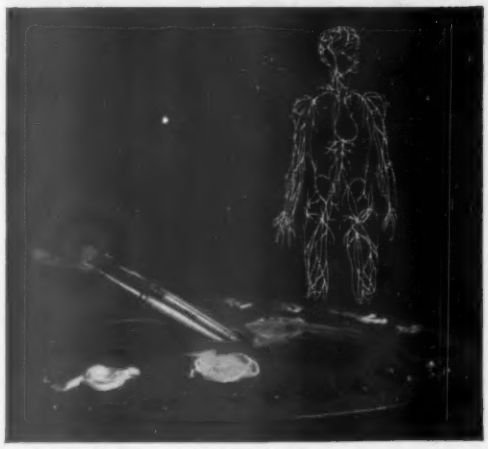
SPECIALISTS IN

ELECTRODYNE

MEDICAL ELECTRONICS

ELECTRODYNE CO., INC. 20 Endicott Street, Norwood, Mass.

basic to the Art of hypertension management



moderil®
brand of rescinnamine

a refinement in rauwolfia alkaloid therapy

Science for the world's well-being™

Pfizer

PFIZER LABORATORIES
Division, Chas. Pfizer & Co., Inc.
Brooklyn 6, New York

IN BRIEF

MODERIL is rescinnamine, a purified rauwolfia alkaloid providing the benefits of reserpine with reduced frequency and/or severitv of certain reserpine side effects. Rauwolfia has been referred to as the first agent to be tried and the last omitted in antihypertensive therapy. When **MODERIL** is given with other antihypertensive agents, the latter may often be administered in lower dosage with fewer undesired reactions.

INDICATIONS: Primary therapy in mild to moderate labile hypertension. In more severe cases, as adjunctive therapy with other agents.

ADMINISTRATION AND DOSAGE: Adjust dosage to minimum level for optimal therapeutic effect. Recommended initial dose—one 0.5 mg. tablet twice a day for two weeks. Significant side effects are unusual with **MODERIL**, but should they occur, reduce dosage to one 0.25 mg. tablet twice daily. When optimal hypotensive effects are obtained during initial period, this same reduced dosage or less may be used. If greater hypotensive effects than those observed during this period are required, cautiously increase dose by 0.25 mg. per day (up to 2.0 mg. per day) and consider combined therapy. Doses should be taken after meals to minimize possible adverse effects of increased gastric secretion.

Initial dosage for children 3-12 years of age is up to 0.25 mg. twice daily for one week. Children should be observed closely and when therapeutic effect is achieved, this dose should be reduced by half, i.e., 0.25 mg. daily.

SIDE EFFECTS: Same type as with reserpine but usually with reduced incidence or severity, e.g., mental depression, bradycardia, nightmares, and fatigue. Nasal stuffiness or congestion may occur but usually disappears with discontinuation of the drug or on use of topical vasoconstrictors or antihistamines. Increased frequency of defecation and/or looseness of stools is an occasional reaction. There have been occasional reports of serious hypotension in persons on *Rauwolfia* compounds who undergo surgery with general or spinal anesthesia. It is suggested that **MODERIL** be discontinued two weeks before surgery, when feasible, or other appropriate measures be taken.

PRECAUTIONS: Because rauwolfia preparations may increase gastric secretion, **MODERIL** should be used with caution in patients with a history of peptic ulcer.

SUPPLIED: Yellow, scored, oval tablets of 0.25 mg., bottles of 100 and 500; salmon, scored, oval tablets of 0.5 mg., bottles of 100.

More detailed professional information available on request.

lowers blood pressure drains excess water calms apprehension

Created especially for those patients whose emotional condition complicates the treatment of hypertension and congestive failure

Now the most widely prescribed diuretic-antihypertensive, hydrochlorothiazide, is combined with the most widely prescribed tranquilizer, meprobamate. Called "Miluretic", it constitutes new, effective therapy for hypertension and congestive failure—*especially when emotional factors complicate your treatment.*

What does Miluretic do? Both components are of proven value in hypertension. And in congestive failure, Miluretic induces smooth, continuous diuresis. Miluretic's biggest advantage is that it tranquilizes hypertensive and edematous patients safely and quickly.

Avoids side effects of other antihypertensive agents

Antihypertensive agents derived from Rauwolfia often cause reactions such as depression and nasal congestion; Miluretic does not.

Miluretic is a highly effective, safe combination that gives the physician new convenience in the treatment of hypertension and congestive failure.

new Miluretic

MILTOWN + HYDROCHLOROTHIAZIDE

Available at all pharmacies

Composition: 200 mg. Miltown (meprobamate, Wallace) + 25 mg. hydrochlorothiazide

Dosage: For hypertension, 1 tablet four times a day. For congestive failure, 2 tablets four times a day.

Supplied: Bottles of 50 white, scored tablets

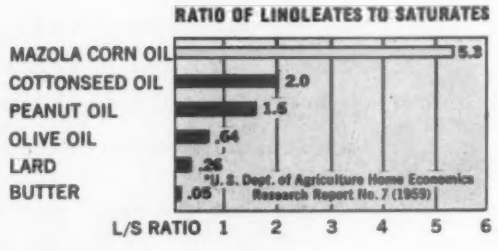
For dietary control of hypercholesterolemia, choose the polyunsaturated oil with the highest Linoleate to Saturate ratio

VEGETABLE OILS *are not all alike.* Each contains certain amounts (characteristic of the oil) of the polyunsaturated glycerides of linoleic acid, which can be effective in lowering serum cholesterol levels, and glycerides of the saturated fatty acids which have the opposite effect. This proportion is called *L/S ratio* (see graph).

In planning diets for hypercholesterolemic patients, it is desirable to replace a substantial portion of the more saturated type of fats, having a low L/S ratio, with oils having a high linoleate content and a high L/S ratio. Balanced meals can be planned containing appreciable amounts of lean meats, poultry and fish, diets more acceptable to patients than stringent low fat diets.

Mazola Pure Corn Oil has an L/S ratio that is *consistently higher than that of any other leading edible oil.*

Thus, where dietary control of hypercholesterolemia is indicated, Mazola Corn Oil is preferred among leading brands... readily available at a reasonable price... instantly acceptable by your patient.

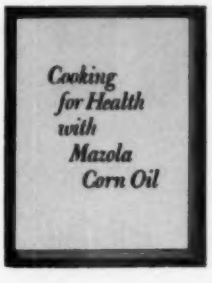


SELECTED BIBLIOGRAPHY—Leading authorities agree that substitution of polyunsaturated for saturated fats in the diet will lower serum cholesterol. The following references reflect current medical opinion. 1. Ahrens, E. H., *et al, J.A.M.A. 170* (18) 2198 (Aug. 29, 1959) 2. Louis N. Katz, Jeremiah Stamler and Ruth Pick, *Nutrition and Atherosclerosis* (1958), p. 108. 3. Boyer, P. A., *et al, J.A.M.A. 170* (3) 257 (May 16, 1959). 4. Jolliffe, N., *A. J. Clin. Nutrition 7*, 451 (1959). 5. Keys, A., *et al., Circulation 19*, 201 (1959).

QUALITATIVE MEASURE OF L/S RATIO. After refrigeration for 96 hours at 33°F, peanut and cottonseed oils have clouded and precipitated. Only MAZOLA (left), having a far lower degree of saturation than other leading vegetable oils, remains unclouded.

FREE DIET GUIDE

"Cooking For Health With Mazola Corn Oil" clearly explains the relation of diet to cholesterol control to your patient. For your copy and a supply of order cards for your patient, fill in the coupon.



COMPOSITION OF MAZOLA CORN OIL

Mazola Corn Oil has the following average composition:

Glycerides of Fatty Acids	Grams/ 100 grams	Grams/ tablespoon
Unsaturates, Total	85 (82-87)	11
Linoleates	54 (52-56)	7
Saturates, Total	11 (9-12)	1.4
Natural Sitosterols	1 (0.9-1.3)	0.14
Natural Tocopherols	about 0.1	0.015
Cholesterol	None	None
Salt (Sodium chloride)	None	None

Calories—125/tablespoon

CORN PRODUCTS COMPANY
10 East 56th Street
New York 22, N. Y.

Please send me a copy of "Cooking For Health With Mazola Corn Oil" and a supply of order cards for my patients.

Name_____M.D.

Address_____

City_____

Zone____ State_____

OF ALL LEADING BRANDS, ONLY MAZOLA IS CORN OIL!

IN SHOCK OF

MYOCARDIAL INFARCTION

INJECTION

ARAMINE®

METARAMINOL

provides combined pressor, myocardium-stimulating effect with no tissue slough reported

ARAMINE "Metaraminol combines strong pressor effect with myocardial-stimulating action . . ."[1]

ARAMINE can be administered for balanced pressor, myocardium-stimulating effect by any desired route—intravenous, intramuscular or subcutaneous—with no reported tissue slough and with minimal risk of causing arrythmias. Repeated injections of ARAMINE appear to elicit no tachyphylactic response.

ARAMINE is always ready for immediate use—no dilution is required. These advantages of ARAMINE make it equally valuable in shock accompanying anaphylaxis, brain damage, infectious disease, hemorrhage, surgery, trauma.

Supplied: in 1-cc. ampuls and 10-cc. vials (10 mg. per cc.).

ARAMINE is a trademark of Merck & Co., INC.

ADDITIONAL information is available to physicians on request. Address Professional Service Department, West Point, Pa.

1. Selzer, A. and Rytand, D.A.: COUNCIL ON DRUGS, Report to Council J.A.M.A. 168:762, (Oct. 11) 1958.


MSD
MERCK SHARP & DOHME
Division of Merck & Co., INC. Philadelphia 1, Pa.

The American Journal of Cardiology

VOLUME VI DECEMBER 1960 NUMBER 6

EDITORIAL

Pooling the Efforts of Soviet and American Cardiologists

THE struggle against cardiovascular diseases occupies an important place in the work of both the Soviet and American public health services. The spread of diseases such as atherosclerosis, myocardial infarction and high blood pressure is great in both countries and, regrettably, their incidence has been climbing steadily during recent decades. The task of medical science is to develop new approaches to the elucidation of the nature of these diseases, their causes of spreading and their effective prophylaxis and treatment. Combined efforts by scientists and physicians of our countries will undoubtedly yield more valuable results than their separate endeavors.

Soviet scientists wholeheartedly acclaimed the conclusion of the agreement on cultural exchanges between the U.S.S.R. and the United States, which provided, among other things, for the cooperation of cardiologists of both countries. What problems could get both Soviet and American scientists working together?

We consider that top priority should be given to clarifying the causes of cardiovascular diseases. Soviet scientists have proved the important role of nervous tension in the development of hypertensive disease. American scientists studying the "epidemiology" of atherosclerosis have established its connection with the diet. We think that an additional study of these factors by joint efforts is required. There are indications that atherosclerosis is not merely a result of consumption of food rich in fat but is also connected with more complex influences of the social environment. Our theory of hypertensive disease, too, should be studied by our American colleagues.

It is also necessary to work out methods for the early diagnosis of atherosclerosis, in particular that of the coronary arteries. It is generally known that often this disease first manifests itself in death resulting from acute myocardial infarction. In the overwhelming majority of patients, however, it is preceded by anatomic narrowing or occlusion of the coronary arteries which proceeds without any symptoms. Bold attempts are being made by American cardiologists to visualize the coronary arteries radiologically, which hold much promise for the future. At a joint symposium it would be possible to discuss the importance of ordinary (instrumental-physiologic) and biochemical research for the diagnosis of the initial stages of atherosclerosis.

We also attach great importance to the creation of a universal classification of cardiovascular diseases. Such a classification will reflect the present level of understanding of pathologic processes and inevitably touch upon questions of morphology, etiology and clinical symptoms of these processes. Such a classification is unattainable without a critical analysis of basic theories advanced by American and Soviet scientists in this field.

Of equal importance is the search for effective medical means of combating hypertension, atherosclerosis and coronary insufficiency. While more or less tangible successes have been attained in the therapy of patients with hypertensive disease over recent years, this cannot be said about the two other diseases. There is a special need for a study by scientists of our countries of methods of combating coronary insufficiency. Last but not least, joint research could result in the development of new radical methods in treating coronary artery disease and its complications.

Prominent American cardiologists will be our guests in the near future. We hope to discuss with them many questions of mutual interest.

PROF. ALEXANDER L. MYASNIKOV
Academy of the Medical Sciences
Moscow, U.S.S.R.

Clinical Studies

Detection of Intracardiac Shunts by an External Surface Counting Technic*

JOHN D. TURNER, M.D., EDUARDO SALAZAR, M.D. *and* RICHARD GORLIN,† M.D., F.A.C.C.

Boston, Massachusetts

THE DETERMINATION of cardiac output by the dilution method without arterial sampling has been validated in man by Pritchard[1] and MacIntyre.[2] This technic has been applied to patients with intracardiac shunts.

Groups working with Nicholson and Wood[3,4] have demonstrated a delayed downslope of the systemic arterial indicator dilution curve in the presence of pulmonary recirculation and early systemic arrival in the presence of pulmonary bypass. These phenomena may be demonstrated by the external isotope counting technic as well.

In 1949 Prinzmetal[5] demonstrated a qualitative aberration from the normal contour of the radiocardiogram in a patient with patent ductus arteriosus. Greenspan, Lester and Marvin[6] demonstrated similar findings in a variety of patients with congenital heart disease. We previously studied[7] a series of patients with intracardiac shunts which were detected by the precordial recording method and an attempt was made to quantify the magnitude of the shunts. The present communication reports this series in detail.

MATERIAL AND METHODS

Twenty-three patients with intracardiac shunts were studied. Twenty-one of these patients had left to right shunts and two had right to left shunts. Fifteen of the twenty-one patients with left to right shunts had atrial septal defects and six had ventricular septal defects, all proved by cardiac catheterization. The ratio of pulmonary blood flow to systemic blood flow ranged from 1.5 to 9.7. Of the two cases with right to left shunt, one patient had an atrial septal defect with high pulmonary vascular resistance and reversed shunt, while the other patient had a pentalogy of Fallot. Ten control subjects were studied. All of them were free of congenital or valvular heart disease.

Radioactive iodinated (human) serum albumin‡ was used as the indicator in all cases. Venipuncture was performed in both arms with No. 18 indwelling needles with stylets. One site was used for injection, the other for drawing blood samples for calibration. Arterial puncture was not necessary. A 3.0 cm. scintillation counter probe§ with a 7.0 cm. collimation was connected in series to a decimal scaler‖ and a count rate computer.¶ The change in concentration of radioactivity as a function of time during the primary circulation was recorded directly on a semilogarithmic# graphic meter which received the count rate computer output.

As recommended by Pritchard[1] and MacIntyre[2], the scintillation counter probe was placed over the fourth intercostal space or fifth rib at the right sternal border to obtain the predominant right heart dilution curves. The superior vena cava and high right atrium (third intercostal space) were avoided because of the possibility of inadequate mixing of the radioactive bolus at these sites. To record predominant left heart dilution curves, the probe was usually

‡ RISA, Abbott Laboratories, North Chicago, Illinois.
§ Model 2270, Beckman Instruments, Berkeley, California.
‖ Model 2001, Beckman Instruments, Berkeley, California.
¶ Model 1600, Beckman Instruments, Berkeley, California.
# Esterline Angus Co., Indianapolis, Indiana, or Varian (G-11A recorder), Palo Alto, California.

* From the Medical Clinics, Peter Bent Brigham Hospital and Department of Medicine, Harvard Medical School, Boston, Massachusetts. This work was supported by grants from the U. S. Public Health Service (N.I.H. H-2637), Kriendler Memorial Foundation, Wyeth Laboratories, Massachusetts Heart Association and the Warner-Chilcott Laboratories.

† Investigator, Howard Hughes Medical Institute.

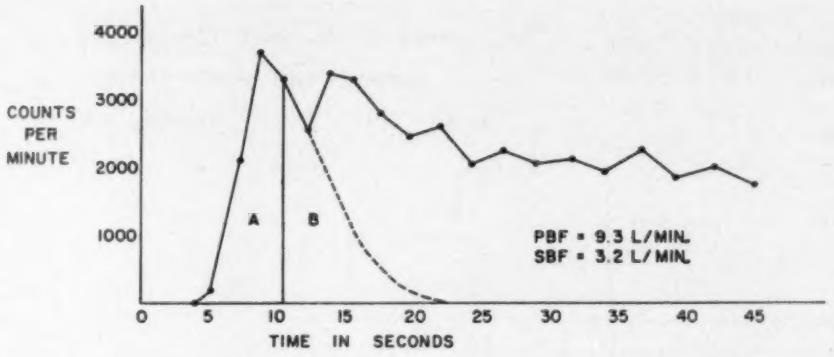


FIG. 1. Linear plot of indicator dilution curve obtained in one of our patients (Table III, Case 12) who had ventricular septal defect with left to right shunt. The scintillation counter probe was placed over the fifth rib at the right sternal border. Pulmonary blood flow (PBF) was estimated as follows: Area A was determined planimetrically while area B was determined by extrapolating the first downslope following peak concentration. The systemic blood flow (SBF) was determined from the predominant left heart dilution curve from the same patient.

placed over the point of maximal impulse. However, it was usually necessary to place the probe more laterally toward the anterior or mid-axillary line in a more horizontal position in patients with large left to right shunts and clockwise rotation of the heart.

A blood sample and graphic background were obtained with the needles in place and the detector probe approximately positioned. The labeled albumin (usually 10 to 30 μc. per injection) was injected rapidly into one of the veins in the arm followed immediately with a rapid flush of 10 to 20 ml. of sterile isotonic saline via a three-way stopcock. The inscribed curve was recorded for a period of thirty seconds after systemic recirculation. An equilibration blood sample was obtained after ten minutes and a graphic recording was made of the same "mixing pool" which was sampled by the detector during the injection of the isotope. Dilution curves over the two ventricles were recorded individually at intervals of ten minutes because dual probes were not available.

The *cardiac output* was determined as described elsewhere.[8] The formula used was as follows:

$$C.O. = \frac{TBV \times FD - B}{CavT}$$

where

$C.O.$ = cardiac output (cc./min.)
TBV = total circulating blood volume (cc.)
FD = ten minute final dilution as recorded on graph (counts/min.)
B = background radioactivity as recorded on graph prior to recording of the dilution curve (counts/min.)
$CavT$ = area under the curve of the primary circulation (counts)

An attempt was made to measure *pulmonary blood flow* in these patients when the first right heart entry and primary isotope decay could be recorded prior to pulmonary recirculation (Fig. 1). Although only three to four points were available on the first rapid downslope, extrapolation of the line through them and measurement of the area was performed on the assumption that this represented primary dilution through the right heart chambers before re-entry of the isotope through the shunt.

Systemic blood flow was derived from the left heart dilution curve by extrapolation of the downslope when it showed a primary decay. Cardiac output was also estimated by the direct Fick method during cardiac catheterization. This was not necessarily simultaneous with the dilution studies.

OBSERVATIONS

Normal Subjects: The contour of the right heart dilution curve was similar in all controls (Fig. 2). The appearance time was short and was followed by a rapid rise to maximal concentration. Then there was a rapid downslope as the isotope cleared the right ventricular chamber. The curve was inscribed until systemic recirculation had occurred.

The morphology of the left heart dilution curve was characteristic and similar in all control subjects (Fig. 3). In the predominant left heart dilution curve the appearance time was delayed by 6 to 10 seconds due to transit of the isotope through the pulmonary circulation. The curve showed a more gradual upslope than the right heart curve because the isotope had been mixed more thoroughly in the pulmonary circulation before it arrived at the left heart. The downslope was similarly more gradual and prolonged.

Table I shows the cardiac output values obtained by probe placement over the right and left chambers of the heart in the ten

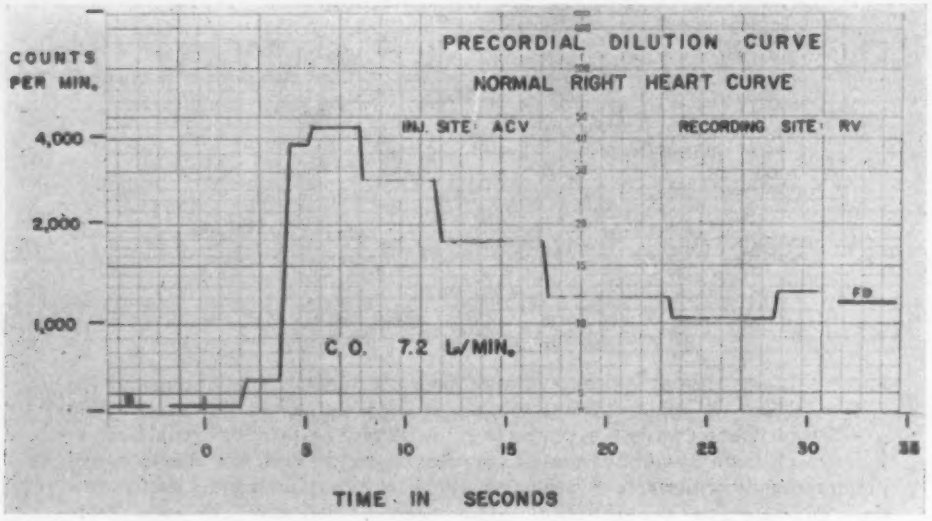


FIG. 2. Normal right heart indicator dilution curve obtained in the first control subject (Table 1). I^{131} albumin was injected into the right antecubital vein (ACV). The probe was placed over the chambers of the right heart (RV). A linear plot of the curve was obtained by joining the mid-points of the horizontal bars on the graph above. *C.O.* = cardiac output (L./min.)

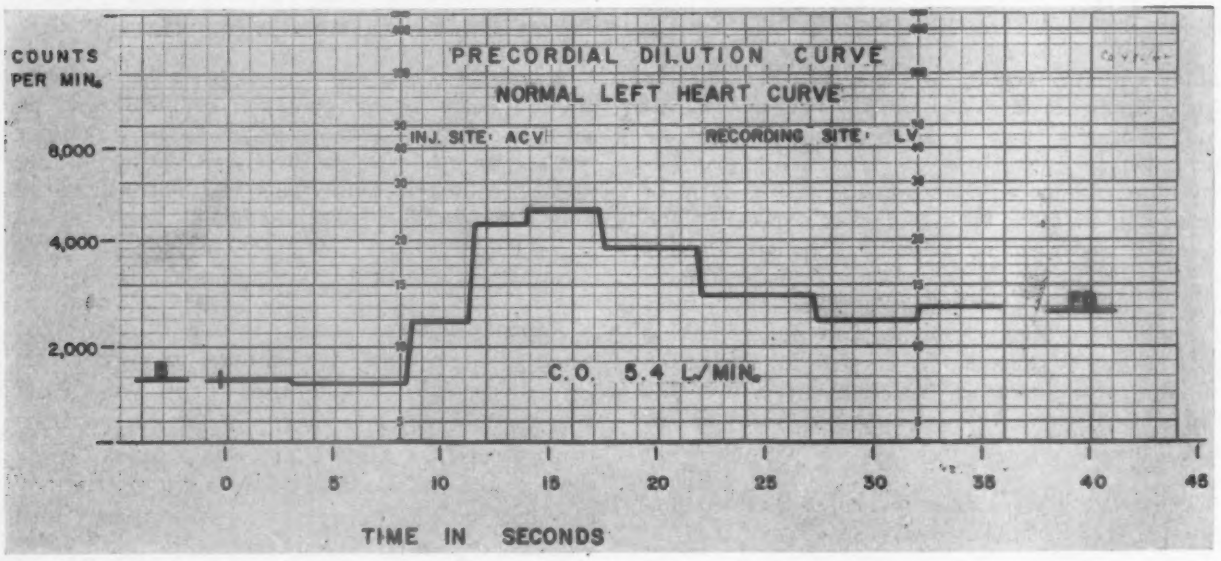


FIG. 3. Normal left heart indicator dilution curve obtained in the tenth normal subject. The scintillation counter probe was placed over the point of maximal impulse with 30 degrees of medial angulation (LV). Injection was into the right antecubital vein (ACV).

normal subjects. A more extensive series with comparison to other methods is reported elsewhere.[9]

Left to Right Shunts: In *atrial septal defects* the morphology of the dilution curve obtained over the right precordium was altered due to repeated shunting of the isotope from the left to the right atrium. The external isotope counting technic recorded the pulmonary recirculation directly (Fig. 4A). After peripheral venous injection the appearance time and rapid rise to maximal concentration were normal. The remainder of the curve shows an early rapid downslope followed by multiple "recirculation humps" and the final downslope is prolonged and delayed. It is important to note that evidence for pulmonary recirculation was seen during the first 6 to 10 seconds after peak concentration was reached, *i.e.*, at the same time or before the peak concentration occurred in the *left*-predominant dilution curve for that patient (Fig. 4B).

TABLE I
Precordial Indicator Dilution Technic

Normal Subjects	Cardiac Output* (L./min.)	
	Right	Left
1	4.8	4.6
2	4.9	4.9
3	6.8	7.1
4	7.2	6.7
5	6.0	5.6
6	7.3	6.7
7	7.4	6.7
8	10.6	9.4
9	6.9	7.3
10	4.3	5.4

* Cardiac output determinations were performed ten minutes apart with minimal apparent change in the state of the patient. The greatest deviation between values obtained from the two precordial sites was 26 per cent with an average of 9 per cent. Simultaneous performance of right and left precordial dilution curves with dual probes would be preferable.

This type of curve contour was found in the right-predominant isotope dilution curve in *all* fourteen patients with atrial septal defects. The left-predominant isotope dilution curves in all these patients displayed a gradual rise and a prolonged downslope.

TABLE III
Arterial Appearance Time of Indicator in Localization of Right to Left Shunt to the Atrium

Site		Arrival Time (seconds)
Injection	Sampling	
Right atrium	Brachial artery	3
Right ventricle	Brachial artery	12
Pulmonary artery	Brachial artery	13.2

Successful surgical closure of the septal defect restored the right-predominant curve to normal (Figure 5A and B).

Figure 6A illustrates the right heart curve in a patient with *ventricular septal defect*. The altered curve contour was the same in both atrial and ventricular defects. The left-predominant dilution curves in the patients with ventricular septal defects showed "smearing" of the normal contour (Fig. 6B).

This same phenomenon has been seen in one patient with hemodynamically significant *tricuspid insufficiency* which is a form of right to right shunt.

In one patient with ventricular septal defect with a 30 per cent left to right shunt the method failed to reveal the presence of

TABLE II
Comparison of Methods: Left to Right Shunts

Subjects	Pulmonary Blood Flow (L./min.)		Systemic Blood Flow (L./min.)		Ratio of PBF/SBF	
	Precordial	Fick	Precordial	Fick	Precordial	Fick
ASD*						
1	11.8	14.7	5.3	5.5	2.2	2.7
2	12.6	15.8	6.0	5.0	2.1	3.2
3	11.1	17.1	5.3	4.6	2.1	3.9
4	13.6	13.7	4.7	2.9	2.9	4.7
5	11.2	14.3	1.9	3.1	5.9	4.6
6	11.3	9.5	2.5	2.6	4.0	3.7
7	—	11.3	4.1	3.7	—	3.1
8	—	17.4	3.9	3.3	—	5.3
9	12.8	28†	3.0	2.9	4.3	9.7†
VSD*						
10	11.8	13.6	3.7	4.7	2.9	2.9
11	11.8	18.3	5.4	5.5	2.2	3.3
12	13.2	41.2†	2.8	4.6	4.7	8.9†
13	13.4	12.3	2.6	5.3	5.1	2.4

* ASD = atrial septal defects; VSD = ventricular septal defects.
† The pulmonary arteriovenous oxygen differences were so narrow (6 and 7.5 cc./L., respectively) as to preclude accurate estimation of shunt by the Fick method.

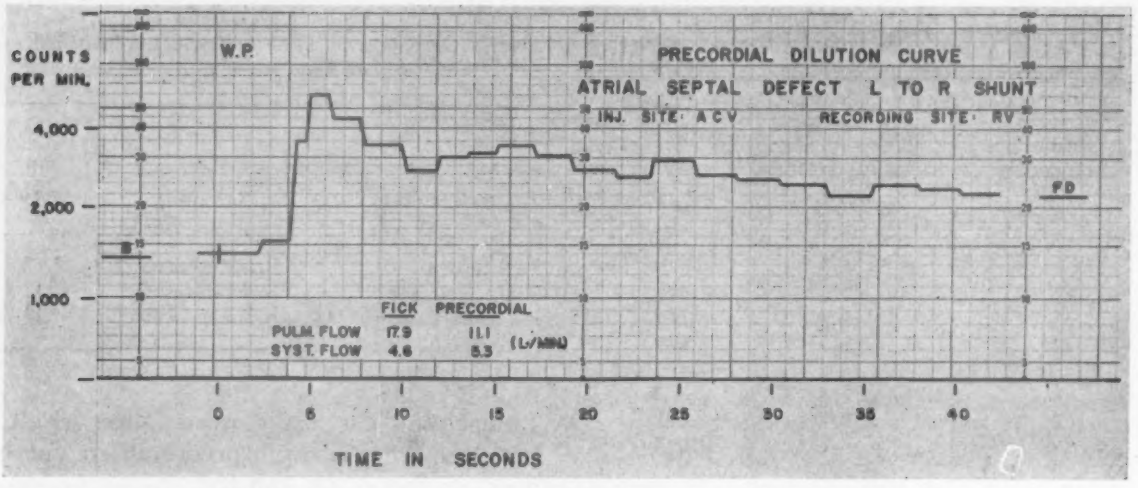


FIG. 4A. Right-predominant dilution curves obtained in (Case 3, Table II), a patient who had atrial septal defect with left to right shunt. I^{131} albumin was injected into the antecubital vein (ACV) and the scintillation counter probe was placed over the right ventricle (RV). Note the multiple "recirculation humps" on the downslope. This type of pattern was consistently observed in the right heart dilution curves in patients with left to right shunts.

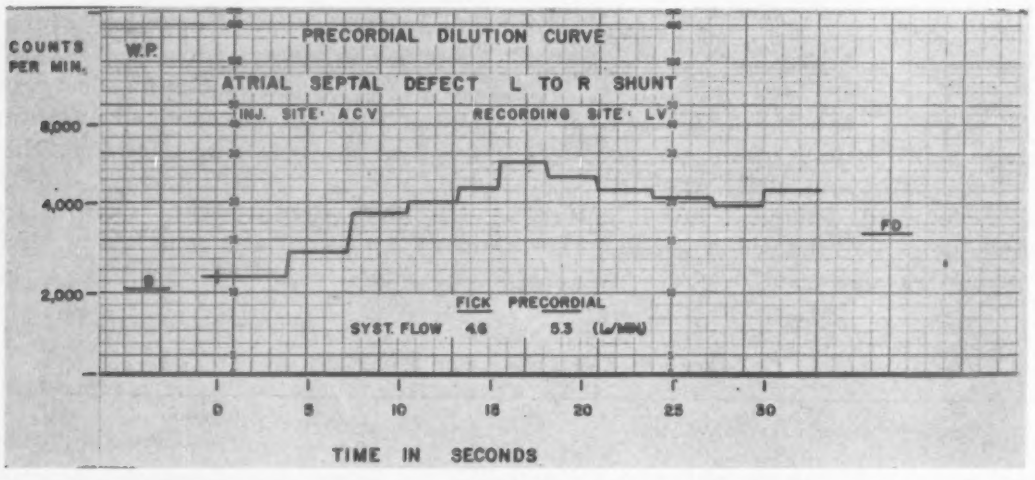


FIG. 4B. Left-predominant dilution curve obtained in the same patient. The probe was placed at the anterior axillary line with 60 degrees of medial angulation (LV) and I^{131} albumin was injected into the right antecubital vein (ACV).

shunt in spite of multiple precordial sites of probe placement.

In one patient with *patent ductus arteriosus*, curves written over the right ventricle were normal, as might be expected. Apparent recirculation through the shunt was detected from curves recorded over the pulmonic area.

Right to Left Shunts: Figure 7 illustrates peripheral venous injection of labeled albumin in a patient with *pentalogy of Fallot*, with the detector probe placed over the left heart chambers. The appearance time was only 3.3 seconds (normal 6 to 10). The right to left shunt at both the atrial and ventricular levels was later confirmed at cardiac catheterization. Most probably, the atrial and not the outflow tract shunt was detected externally. A similar early arrival was observed in a case of *atrial septal defect with reversed shunt*. It is not possible to localize the site of the shunt in these patients with this method. Table III illustrates how intracardiac injection of the isotope at different locations with systemic arterial sampling can determine the site of the shunt.

Quantification of Cardiac Output: Table II includes data about patients in whom a primary downslope could be drawn for estimation of pulmonary blood flow by the external counting method. A Fick output was measured at the same catheterization in each of these. This

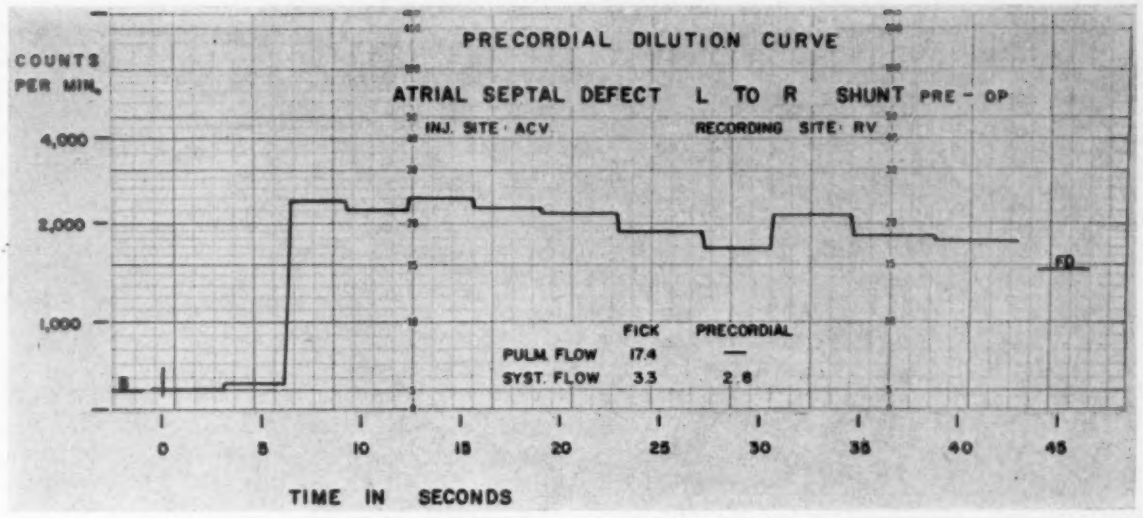


FIG. 5A. Right-predominant dilution curve (RV) obtained in Case 8 (atrial septal defect) prior to surgery. Note the "recirculation humps" on the downslope. The recirculation was so rapid that an initial downslope could not be extrapolated to determine pulmonary blood flow by the precordial method.

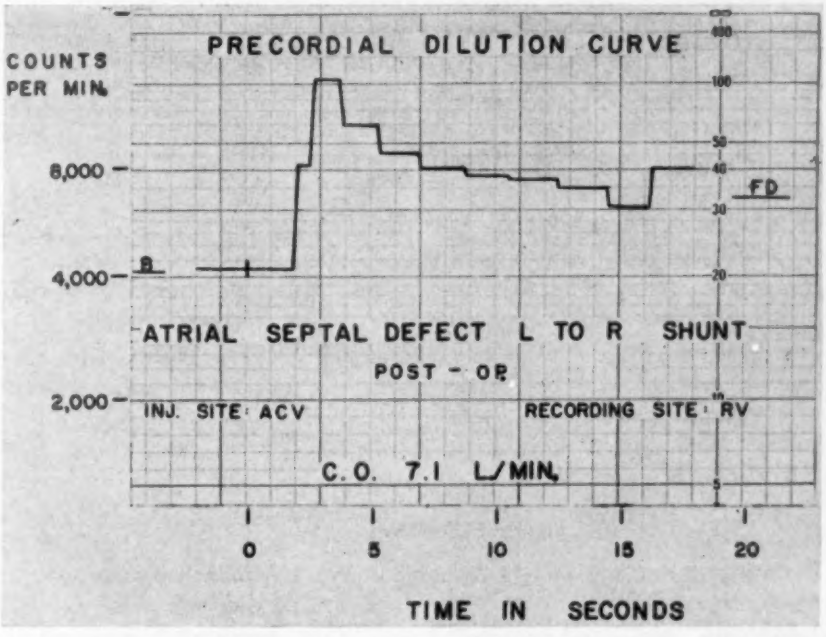


FIG. 5B. Right-predominant dilution curve (RV) in the same patient following surgical repair of the atrial septal defect. The curve contour is now normal in outline. Note the cardiac output increased from 2.8 to 7.1 L./min. following surgery.

comparison of results is only a preliminary attempt at quantification. Three patients were excluded because Fick and isotope studies were performed on different dates; four were excluded because no primary downslope could be drawn. In one patient the curves revealed no shunt which was considered a false negative result. In cases 9 and 12 the pulmonary arteriovenous oxygen difference was so narrow that the Fick blood flows were improbable at 28 and 41 L./min., respectively, while the dilution curves revealed pulmonary blood flows of 12.8 and 13.2 (ratios of pulmonary blood flow to systemic blood flow were 4.3 and 4.7, respectively). In the remaining patients a high pulmonary blood flow was calculated and a reasonable comparison of the ratios of pulmonary blood flow to systemic blood flow was made. It should be emphasized, however, that the demonstration of *qualitative* alteration in the

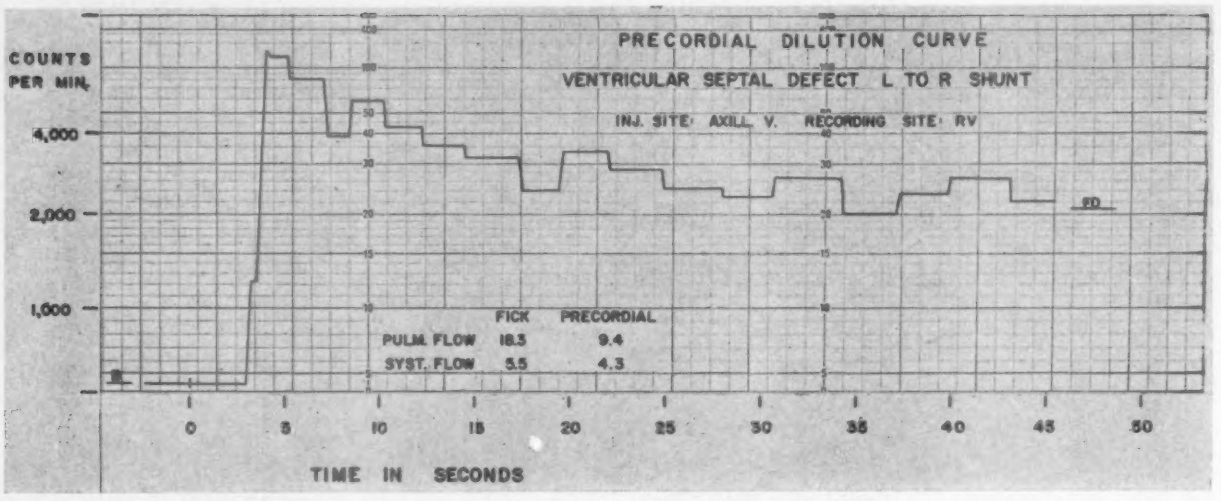


FIG. 6A. Right-predominant dilution curve (RV) in Case 11 (ventricular spetal defect with left to right shunt). The curve morphology was similar to that seen in patients with atrial septal defect and left to right shunt. The multiple "recirculation humps" are well demonstrated on the downslope.

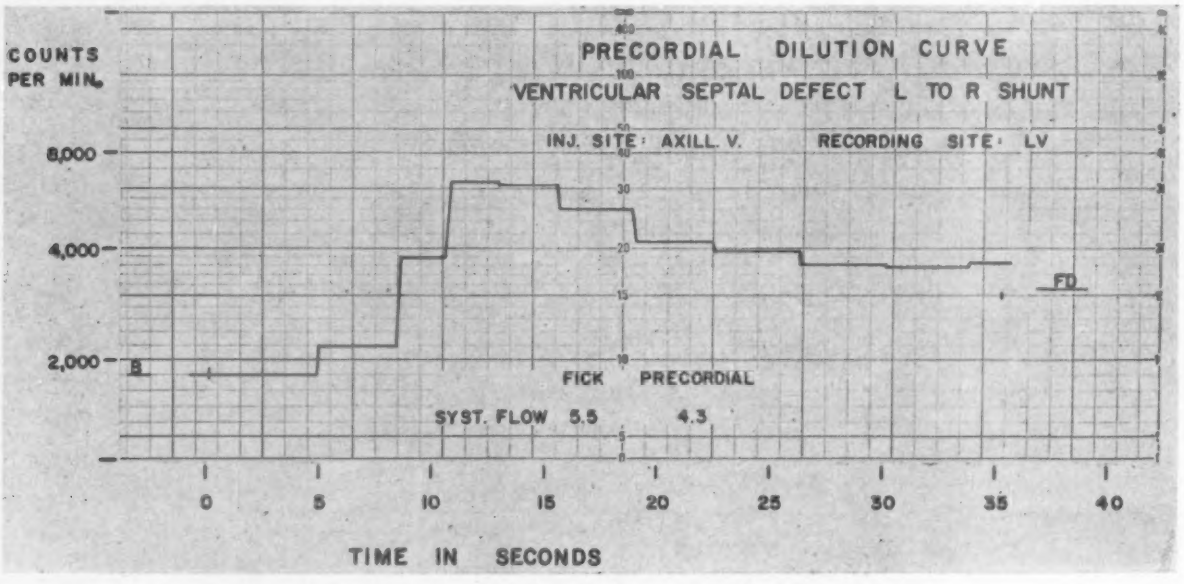


FIG. 6B. Left-predominant dilution curve (LV) in the same patient.

contour of the right-predominant precordial dilution curve was the major factor considered to be of diagnostic importance.

DISCUSSION

Use of an external surface counting technic makes it possible to demonstrate the altered dilution curve contours reported by Nicholson,[3] Broadbent[4] and Swan.[10] Most probably, the recirculation and delayed downslope seen over the right heart is a recording of the primary aberration which results in the characteristic arterial curve described by these authors. Arterial sampling is obviated by the external surface counting technic.

The presence of multiple "recirculation humps" on the downslope of the right-predominant dilution curve is presumptive evidence of a hemodynamically significant left to right shunt; as such, the technic has been used effectively as a screening test prior to cardiac catheterization when intracardiac shunt was suspected clinically. This method cannot be expected to localize the site of the shunt. On the other hand, a patent ductus arteriosus will have normal right heart curves and may possibly be localized by counting along the upper left sternal border.

Limitations of the External Surface Counting Method: The magnitude of the shunt with

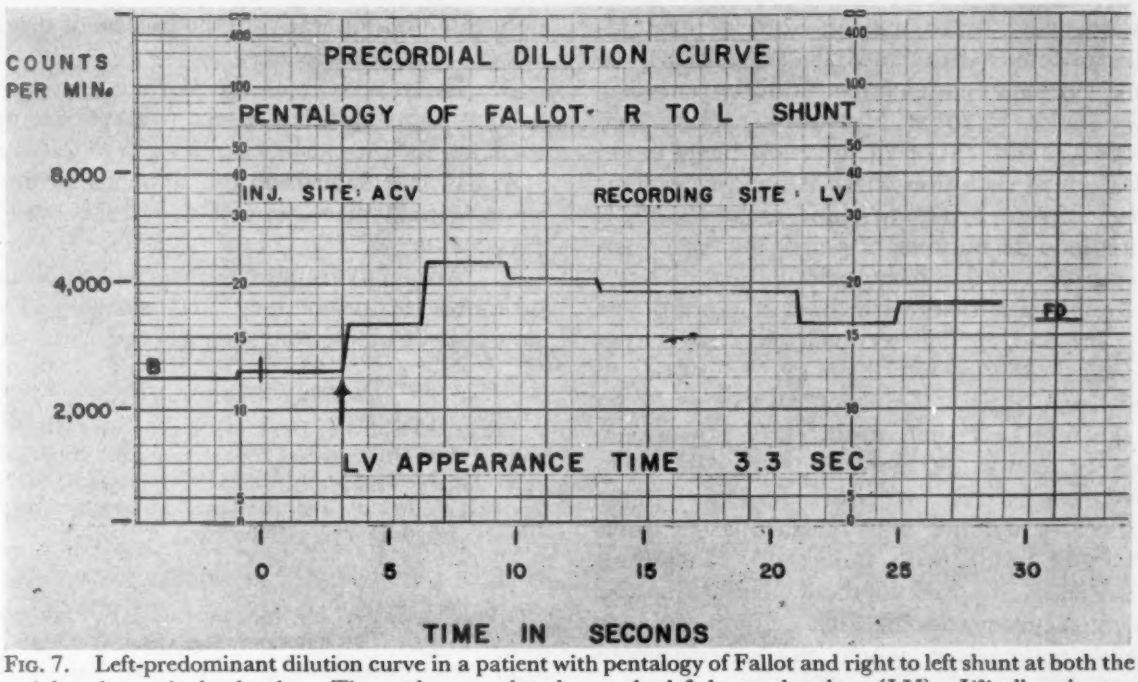


FIG. 7. Left-predominant dilution curve in a patient with pentalogy of Fallot and right to left shunt at both the atrial and ventricular levels. The probe was placed over the left heart chambers (LV). I^{131} albumin was injected into the antecubital vein (ACV). Both right and left heart isotope arrival times were 3.3 seconds.

respect to the total pulmonary blood flow is as important to the external isotope counting method as it is to the dye dilution technic. Wood[11] has pointed out that left to right shunts of 25 per cent or less may be missed with the dye method under the most ideal conditions. In one instance in our laboratory a 30 per cent left to right shunt was missed when we used the precordial technic. Therefore, we assume that left to right shunts smaller than this value may go undetected. Likewise, in small right to left shunts, the amount of the isotope arriving prematurely in the chambers of the left heart may be insufficient to be detected by the scintillation counter probe.

Trailing of the dose and "smearing" of the dilution curve described by Wood can be minimized by following the injection of the isotope with an immediate rapid flush of 10 to 20 ml. of isotonic saline to insure rapid entry of the injectate into the central circulatory system.

Probe placement is a critical factor. Many of the difficulties encountered with the external isotope method arise either from placement of the probe over the great veins or from failure to stress one ventricular clearing chamber over the other. Placement over the superior vena cava can result in an early rapid peak and downslope as well as a spuriously high calculation of pulmonary blood flow. This can be due to inadequate mixing prior to right heart entry or to probe sampling at the time of equilibration of a larger vascular mixing volume (left atrium) than that in which the original curve was diluted (superior vena cava only). Placement of the probe over the mid-precordium so that both ventricles contribute equally to the dilution curve results in a twin-peaked curve which often has a biphasic downslope. If the left heart chambers contribute only in part to the right heart curve, a second much smaller peak may occur on the downslope and falsely suggest a left to right shunt in a normal subject. However, as long as the first "recirculation hump" occurs at the time of (or preferably, *before*) the peak concentration of the left heart curve (usually 6 to 10 seconds) and is then followed by other "recirculation humps," evidence for pulmonary recirculation is probably valid. Similarly, contribution of the right heart to the left heart dilution curve may result in apparent premature arrival of the isotope at the left heart and produce false positive evidence for right to left shunt. Although largely a process of trial and error, satisfactory curves can usually be obtained if the superior vena cava, high right atrium, and mid-precordium are avoided and the two diluting patterns separated. This can be accomplished by placement of the probe as close to the lower right sternal border as feasible to obtain a predominant right heart

dilution curve or to the left anterior or mid-axillary line (with medial angulation) to obtain a predominant left heart dilution curve.

Comparison of Blood Flows in the Presence of Shunt: Quantification of the right heart blood flow from the dilution curve is open to various sources of error. The first and most obvious is an inadequate number of points on the downslope prior to pulmonary recirculation. Therefore, only those cases with three or more points were included. The second objection is that inadequate mixing may have occurred prior to right heart entry. This would seem excluded by the fact that such rapid early downslopes were not seen in our normal patients in whom poor mixing was an equal hazard. Some evidence of validity may be gleaned by comparison of results with pulmonary blood flow measured by the Fick method. Unfortunately, gross inaccuracies in the Fick method preclude careful comparison when the arteriovenous oxygen difference is narrow (Case 9).

Systemic blood flow was estimated from the left heart curve. This curve demonstrated the "smearing" of the increased mixing pool of recirculation through the lungs and the two ventricles, and represented, as does the systemic arterial dilution curve, blood flow delivered by the left heart to the periphery. The re-entry of the isotope from pulmonary circulation, although occasionally observed, was usually lost in the attenuation of the curve (and long systemic downslope) with respect to time. Strict comparison to the Fick method was precluded because determination of systemic blood flow (as estimated from the superior and inferior vena caval oxygen samples and not from mixed venous values) was undoubtedly inaccurate.

SUMMARY

1. Intracardiac shunts were detected by an external surface counting technic in twenty-three patients. Precordial indicator dilution curves were recorded over each ventricle separately.

2. In the absence of tricuspid valvular disease, the presence of multiple "recirculation humps" on the right-predominant dilution curve was evidence for a left to right shunt. The technic did not differentiate between atrial or ventricular septal defects, and probably cannot clearly demonstrate shunts of less than 30 per cent. It can be used effectively as a screening test for cardiac catheterization and to determine postoperatively the success of surgical closure of septal defects.

3. Early arrival of the isotope in the left-predominant dilution curve was presumptive evidence for the existence of a right to left shunt.

4. Proper interpretation depends primarily upon critical placement of the probe over the precordium.

5. Although fraught with error, reasonable estimates of pulmonary and systemic blood flow may be made from these curves.

ACKNOWLEDGEMENTS

We are indebted to Dr. Lewis Dexter who kindly permitted us to study some of his patients and to Drs. Norman Brachfeld, Joseph V. Messer, William A. Neill, Herbert J. Levine and Richard J. Wagman for individual case studies reported herein.

REFERENCES

1. PRITCHARD, W. H., MACINTYRE, W. J. and MOIR, T. W. The determination of cardiac output by the dilution method without arterial sampling. II. Validation of precordial recording. *Circulation*, 18: 1147, 1958.
2. MACINTYRE, W. J., PRITCHARD, W. H. and MOIR, T. W. The determination of cardiac output by the dilution method without arterial sampling. I. Analytical concepts. *Circulation*, 18: 1139, 1958.
3. NICHOLSON, J. W., III, BURCHELL, H. B. and WOOD, E. H. A method for the continuous recording of Evans blue dye curves in arterial blood and its application to the diagnosis of cardiovascular abnormalities. *J. Lab. & Clin. Med.*, 37: 353, 1951.
4. BROADBENT, J. C., CLAGETT, O. T., BURCHELL, H. B. and WOOD, E. H. Dye dilution curves in acyanotic congenital heart disease. *Am. J. Physiol.*, 167: 770, 1951.
5. PRINZMETAL, M., CORDAY, E., SPRITZLER, R. J. and FLIEG, W. Radiocardiography and its clinical applications. *J. A. M. A.*, 139: 617, 1949.
6. GREENSPAN, R. H., LESTER, R. G. and MARVIN, J. F. Isotope circulation studies in congenital heart disease. *Radiology*, 69: 106, 1957.
7. TURNER, J. D., SALAZAR, E. and GORLIN, R. Detection of intracardiac shunts by an external surface counting technique. *Clin. Res.*, 7: 230, 1959.
8. BOZER, J. M. and GORLIN, R. Cardiac output measured by radioactive indicator. In: Methods in Medical Research, vol. 7, p. 70, Chicago, 1958. Year Book Publishers.
9. GORLIN, R., MACLEOD, C. and BOPP, P. Measurement of cardiac output by a direct writing surface scintillation technique. *Clin. Res.*, 6: 215, 1958.
10. SWAN, H. J. C. and WOOD, E. H. Localization of cardiac defects by dye dilution curves recorded after injection of T-1824 at multiple sites in the heart and great vessels during cardiac catheterization. *Proc. Staff. Meet. Mayo Clin.*, 28: 95, 1953.
11. HETZEL, P. S., SWAN, H. J. C. and WOOD, E. H. The applications of indicator dilution curves in cardiac catheterization. In: Intravascular Catheterization. Edited by ZIMMERMAN, H. Springfield, Ill., 1959. Charles C Thomas Co.

Splitting of the Second Heart Sound*

HAROLD A. SHAFTER, M.D.†
Chicago, Illinois

ASYNCHRONOUS closure of the aortic and pulmonary valves accounts for splitting of the second heart sound. Nearly one hundred years ago, Potain[1] recognized splitting of the second heart sound during normal inspiration. Later, Leatham and Towers[2] showed that closure of the aortic valve precedes closure of the pulmonary valve. The appearance or increased magnitude of the splitting with inspiration was ascribed to delay in the pulmonary component reflecting prolongation of right ventricular systole with increased stroke volume due to augmented filling of the right ventricle from the large systemic venous reservoir.[2,3]

Boyer and Chisholm[4,5] recently discovered that earlier closure of the aortic valve contributed equally with later closure of the pulmonary valve to increase the magnitude of splitting of the second heart sound during inspiration. In explanation of this finding they cited physiologic studies[6,7] which they believed to be consistent with inspiratory shortening of left ventricular systole.

Splitting of the second heart sound in patients with uncomplicated atrial septal defect is usually abnormal in two respects:[8] First, it is obvious in expiration and is frequently more than 0.03 second which is a finding rare in normal people. Second, there is little or no increase in the magnitude of the splitting during inspiration. These abnormalities were thought to be due to relative prolongation of right ventricular systole because of the difference between right and left sided flows.[8] It was assumed that there was no further filling of the right ventricle during inspiration in the presence of a large left to right shunt.[9] Boyer and Chisholm[10] recently reported, however, that the pulmonary component of the second sound in patients with atrial septal defect showed movement during respiration within the range for normal subjects. The aortic component either was fixed or paradoxically moved at a later point during inspiration, thus accounting for the "fixed" splitting.

The purpose of this study was to verify the findings of Boyer and Chisholm concerning movement of the two components of the second heart sound in normal subjects and in patients with atrial septal defect and to investigate the mechanisms involved.

MATERIAL AND METHODS

The subjects of this study were as follows: (1) fifteen subjects with normal cardiovascular systems, including eight young adult volunteers, one adult with Reiter's syndrome, one normal child and five children convalescing from illness not related to the cardiovascular system; (2) sixteen patients (including ten children) who had atrial septal defects without heart failure (Table II); (3) four patients (including one child) whose atrial septal defects had been closed surgically nine to twelve months previously; (4) a young adult with anomalous connection of the right pulmonary veins to the right atrium and probably an intact atrial septum; (5) six children with ventricular septal defect; (6) two adults, who were not in heart failure, with electrocardiograms showing a pattern of complete right bundle branch block of unknown etiology; and (7) one young adult with wide splitting of the second heart sound, normal electrocardiogram and normal findings at catheterization of the right side of the heart.

The diagnosis of atrial septal defect was confirmed in one patient at surgery. In all the others with atrial septal defect, except Case 13 (Table II) (total anomalous pulmonary venous connection to the left innominate vein), a cardiac catheter was passed from right atrium to left atrium and a left to right shunt was demonstrated at atrial level. The diagnosis in the patient with anomalous venous connection to the right atrium was made by cardiac catheterization. The catheter was passed into all three lobes of the right lung from the lateral border of the right atrium, and the left atrium was not entered. Curves from injection of Evans blue dye into the right and left pulmonary arteries were typical of anomalous drain-

* From the Cardiac Department, St. George's Hospital, London, England.
† Present address: University of Illinois College of Medicine, Chicago, Illinois.

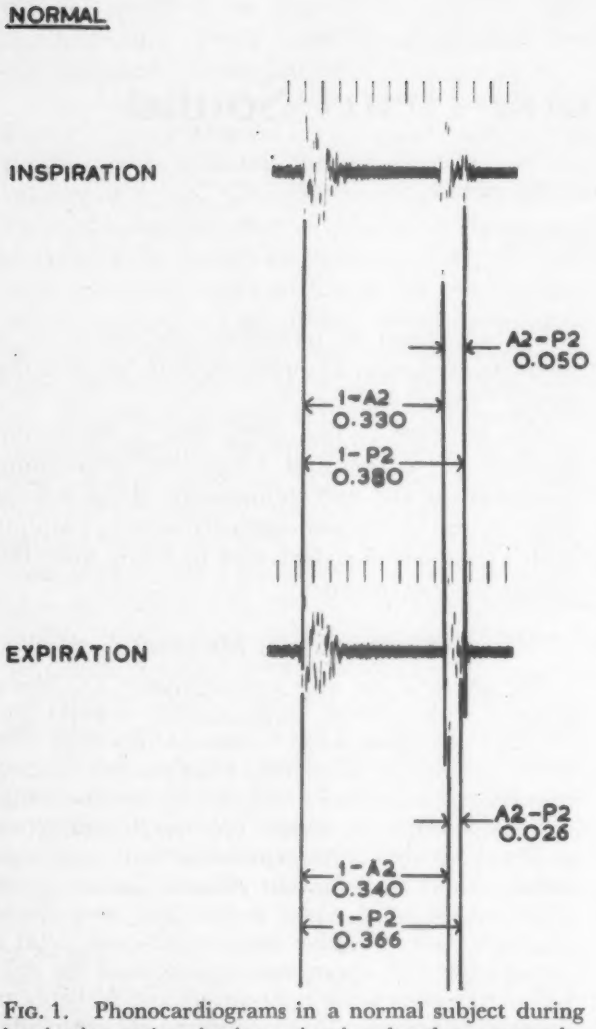


FIG. 1. Phonocardiograms in a normal subject during inspiration and expiration. Aortic valve closure precedes pulmonary valve closure. The interval between the first heart sound and aortic valve closure sound (1-A_2) increases during expiration; the intervals between the first sound and pulmonary valve closure sound (1-P_2) and between aortic valve closure and pulmonary valve closure sounds (A_2-P_2) decrease. Numerals indicate the duration of the intervals in seconds. Paper speed is 100 mm./sec. Time lines are 0.04 second apart.

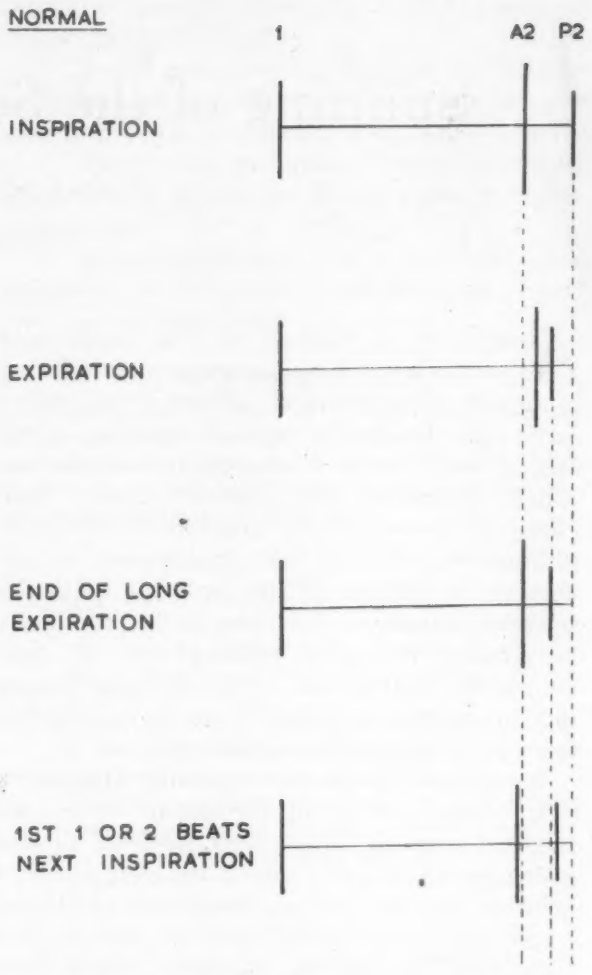


FIG. 2. Diagram representing the relative positions of the first heart sound (1) and the two components of the second heart sound, aortic valve closure sound (A_2) and pulmonary valve closure sound (P_2), in normal subjects during inspiration, expiration, at the end of a prolonged expiration and at the beginning of the next inspiration. A_2 and P_2 are in the same position relative to the first heart sound at the end of a long expiration as during previous inspiration and expiration, respectively. (See text.)

age of the right pulmonary veins into the right atrium with intact atrial septum.[11] Of the six children with ventricular septal defect, three had detectable left to right shunts. The diagnosis in the other three was made by selective cineangiocardiogram.[12]

Graphic Tracings: The subjects reclined on a bed with the chest about 60° to 80° from the horizontal. On a multichannel photographic Cambridge recorder the following were recorded simultaneously at paper speed of 100 mm. per second: (1) heart sounds, usually from two separate areas on the chest for optimal recording of both first and second heart sounds; (2) electrocardiogram; (3) 250 c.p.s. time signal; and (4) respirations. Most subjects were unaware that respirations were being recorded and no instructions were given about the rate or depth of breathing, except in two of the adult volunteers, three of the children with atrial septal defect (Cases 7, 10 and 14, Table II) and the patient with anomalous pulmonary venous connection to the right atrium. Their breathing was voluntarily regulated to allow study of the effect on the heart sounds of prolonged expiration (increased two to three times), prolonged inspiration and variation in rate or depth of respirations. The time signal was generated by an electrical signal generator and was exactly five times the frequency of the electrical mains alternating current frequency (50 ± 0.1 c.p.s. in London), providing time lines at 4 millisecond intervals (0.004 second).

Phonocardiograms were acceptable for measurement only if there were an early fast or high frequency

TABLE I
Second Heart Sound during Inspiration in Fifteen Normal Subjects

Subjects	Maximum Change (msec.)			$\frac{1\text{-}A_2}{1\text{-}P_2} \times 100$ (%)
	1-A_2	1-P_2	A_2-P_2	
Adults				
Mean	−14.1	+15.7	+28.2	96
Range	(−8 to −22)	(+9 to +25)	(+16 to +44)	(52 to 150)
Children				
Mean	−10.3	+17.3	+26.6	61
Range	(−7 to −15)	(+13 to +21)	(+20 to 34)	(33 to 100)
Entire Group				
Mean	−12.6	+16.3	+27.7	77
Range	(−7 to −22)	(+9 to +25)	(+16 to +44)	(33 to 150)

component of the first heart sound and fast components of both aortic and pulmonary valve closure sounds, consistent throughout the respiratory cycle (Fig. 1). The following intervals were measured through at least three consecutive respiratory cycles with an accuracy of ±0.002 second: (1) first heart sound to aortic valve closure sound (1-A_2); (2) first heart sound to pulmonary valve closure sound (1-P_2); and (3) aortic valve closure sound to pulmonary valve closure sound (A_2-P_2) (Fig. 1). The maximum respiratory variations in these intervals were calculated.

RESULTS

Normal Subjects: The results are listed in Table I. During respiration, the aortic valve closure sound (A_2) and the pulmonary valve closure sound (P_2) moved in opposite directions. In general, earlier closure of the aortic valve contributed slightly less than later closure of the pulmonary valve to the inspiratory increase in splitting of the second heart sound. There was no significant difference between children and adults in the average magnitude of respiratory motion of A_2 and P_2 or in the mean maximum inspiratory increase in splitting of the second sound (A_2-P_2), although the respiratory rate varied from 12 to 23 per minute in various subjects.

In the children, however, the average ratio of change in 1-A_2 to change in 1-P_2 was significantly less than in adults (two and a half times the standard error of the difference between the means). In five of the six children, A_2 moved less than P_2, and in one the movement was equal.

In two adults earlier A_2 contributed more than later P_2 to increased splitting of the second sound in inspiration. One of these adults was studied a second time, however, and A_2 and P_2 moved an equal degree. Four other adults showed movement of A_2 and P_2 of equal magnitude.

Increased depth of respiration resulted in greater inspiratory splitting of the second heart sound. A_2 became earlier and P_2 later than when the respirations were more shallow.

The results of a single prolonged expiration in two of the normal adults are shown diagrammatically in Figure 2. P_2 tended to assume the same position as in the preceding expirations or a slightly earlier position. After becoming later as in the preceding expirations, A_2 moved toward the first heart sound as expiration continued. It reached a position at, or earlier than, its previous inspiratory positions. With the next inspiration, P_2 became later but A_2 moved a few milliseconds toward the first heart sound and then became later with the next one or two beats as inspiration continued.

With a single prolonged inspiration, A_2 initially moved toward the first heart sound. As inspiration continued, it began to move away from the first sound. P_2 became later during most of inspiration but then slightly earlier as inspiration was prolonged.

Atrial Septal Defect: Individual data and means are listed in Table II. The outstanding difference between this group and the normal group was in the behavior of A_2 during respiration (Fig. 3.) A_2 was uniformly earlier in inspiration and later in expiration in normal subjects; in twelve of the sixteen patients with atrial septal defect (ASD) A_2 became later in inspiration and earlier in expiration. P_2 occurred later in inspiration as in normal subjects. Since P_2 moved more than A_2, the splitting (A_2-P_2) increased with inspiration.

TABLE II

Second Heart Sound during Inspiration in Sixteen Patients with Atrial Septal Defect (ASD)

Case No.*	Age, Sex	Diagnosis	Pulmonary/ Systemic Blood Flow	Pulmonary Artery Pressure S/D (M) (mm. Hg)	Maximum Change (msec.)		
					$1\text{-}A_2$	$1\text{-}P_2$	$A_2\text{-}P_2$
1	24, F	ASD	1.8/1	10/2 (4)	+7	+17	+14
2	48, F	ASD; RBBB†	3/1	48/15 (25)	+19	+29	+12
3	54, F	ASD	2/1	85/25	+14	+20	+9
4	36, F	ASD	0.85/1	70/30 (47)	+14	+17	+5
5	38, M	ASD; RBBB	3/1	23/7 (17)	+8	+12	+4
6	48, M	ASD	2/1	35/7 (20)	−2	+9	+9
Mean (adults)					+10.0	+17.3	+8.8
7	10, F	ASD	3/1	17/8 (12)	+12	+40	+29
8	11, M	ASD	2.3/1	31/11 (19)	+11	+19	+9
9	7, F	ASD	2.7/1	22/8	+7	+9	+6
10	8, F	ASD	1.8/1	15/5	+7	+12	+6
11	13, F	ASD; anomalous PV(RA)‡	2.7/1	23/5 (13)	+3	+6	+3
12	16, M	ASD	2.7/1	22/12 (16)	+6	+6	+2
13	14, M	Totally anomalous PV§	2.1/1	27/10	+7	+8	+2
14	6, F	ASD	2/1	17/4 (9)	−7	+9	+9
15	15, F	ASD: rheumatic carditis	1.3/1	22/9	−8	+6	+6
16	18, M	Anomalous PV (SVC)‖ ASD? patent foramen ovale?	2.3/1	15/5 (10)	−7	+7	+12
Mean (children)					+3.1	+12.2	+8.4
Mean (entire group)					+5.7	+14.1	+8.6

* Cases 1 through 6 are adults; Cases 7 through 16 are children.
† Complete right bundle branch block.
‡ Anomalous connection of right pulmonary veins to right atrium.
§ Total anomalous pulmonary venous connection to the left innominate vein.
‖ Anomalous connection of the right pulmonary veins to the superior vena cava.

However, the mean increase was much less than in the normals (difference between means = seven and a half times standard error of difference between means). In twelve of sixteen patients $A_2\text{-}P_2$ increased less than 10 msec. (0.010 sec.). Only one patient (Case 7) showed an inspiratory increase of $A_2\text{-}P_2$ within the range for normal subjects.

Although there was a tendency for less respiratory movement of P_2 in children with ASD than in normal children or adults with ASD, the differences were not significant. Adults with ASD showed as much movement of P_2 as normal adults.

In four patients with atrial septal defect the behavior of A_2 was different from that in the others. In one patient (Case 6, Table II) A_2 did not move significantly during respiration. In Case 16, a patient with anomalous pulmonary venous drainage of the right lung into the superior vena cava, A_2 behaved as in the normal group. In each of the other two patients (Cases 14 and 15) A_2 became earlier at the beginning of inspiration and later during the remainder of inspiration and sometimes through early expiration. Slowing the rate of respiration in Case 14 did not alter this pattern.

Effects of a single prolonged expiration were studied in Cases 7, 10 and 14. (Fig. 4.) When expiration was prolonged two to three times, A_2 and P_2 became earlier together. At the

end of this expiration, 1-A_2 and 1-P_2 intervals were essentially the same as during previous expirations. Both A_2 and P_2 became later simultaneously with the next inspiration.

Surgically Repaired Atrial Septal Defect: All four patients showed splitting of the second heart sound of at least 0.030 second in expiration, although none had electrocardiograms meeting all the criteria for complete right bundle branch block.[13] All four had respiratory movements of A_2 and P_2 similar to the normal subjects in magnitude and identical in direction.

Anomalous Connection of the Right Pulmonary Veins to the Right Atrium with Intact Atrial Septum: Maximum respiratory movement of P_2 was only 4 msec. less than any other subject. A_2-P_2 increased 6 msec. with inspiration. At the beginning of expiration, 1-A_2 was least. When inspiration following a prolonged expiration, 1-A_2 remained unchanged as 1-P_2 increased for two beats; then 1-A_2 increased also (A_2 became later).

Ventricular Septal Defect: All the patients studied were similar to the normal group.

Complete Right Bundle Branch Block: As in the normal subjects, A_2 became earlier and P_2 later during inspiration. One of the subjects showed movement of A_2 almost three times that of P_2; mean change of 1-A_2 was 17 msec.; 1-P_2, 6 msec.

The patient with wide expiratory splitting of the second heart sound (0.05–0.06 sec.) and normal findings at catheterization of the right side of the heart showed normal movement of A_2 and P_2.

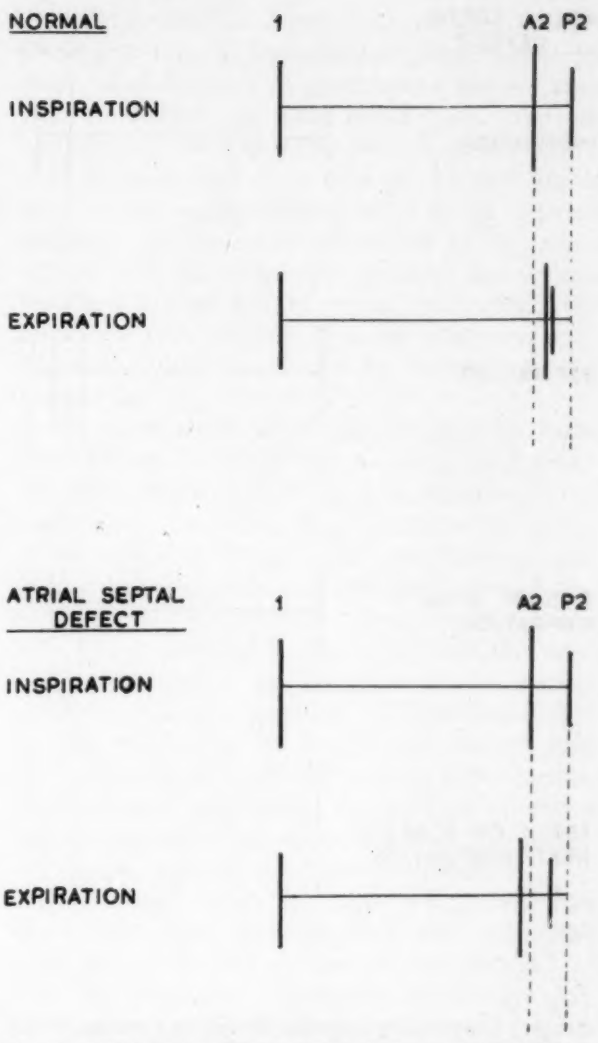


FIG. 3. Diagram comparing the relative positions of the heart sounds during inspiration and expiration in normal subjects and patients with atrial septal defect.

COMMENTS

NORMAL SPLITTING OF THE SECOND HEART SOUND

These studies confirm the findings of Boyer and Chisholm.[4,5] Both earlier closure of the aortic valve (A_2) and later closure of the pulmonary valve (P_2) contribute significantly to the inspiratory increase in splitting of the second heart sound in normal individuals. This is true for children as well as adults. The magnitude of the increase in an individual does not depend upon heart rate[5] but varies with the depth of respiration. As respiratory depth increases, inspiratory increase in splitting of the second heart sound also becomes greater.

Effect of Respiration on Right Ventricular Filling: As has been previously noted, the delay in the pulmonary valve component of the second heart sound during inspiration is probably due to prolonged right ventricular systole.[2,3] Brecher and Hubay[14] have shown in anesthetized dogs with the chest closed that spontaneous inspiration results immediately in an increased venous return to the right side of the heart and in the next systole in an increased right ventricular stroke volume. It is reasonable to assume that right ventricular systole is prolonged slightly from ejecting the augmented volume of blood.

Effect of Respiration on Left Ventricular Filling: An inspiratory decrease in left ventricular stroke volume is not so well established. There is some evidence, however, that has been used to support this concept.[6,7,15] Shuler and coworkers[6] postulated that blood was held in an expanded pulmonary vascular bed during

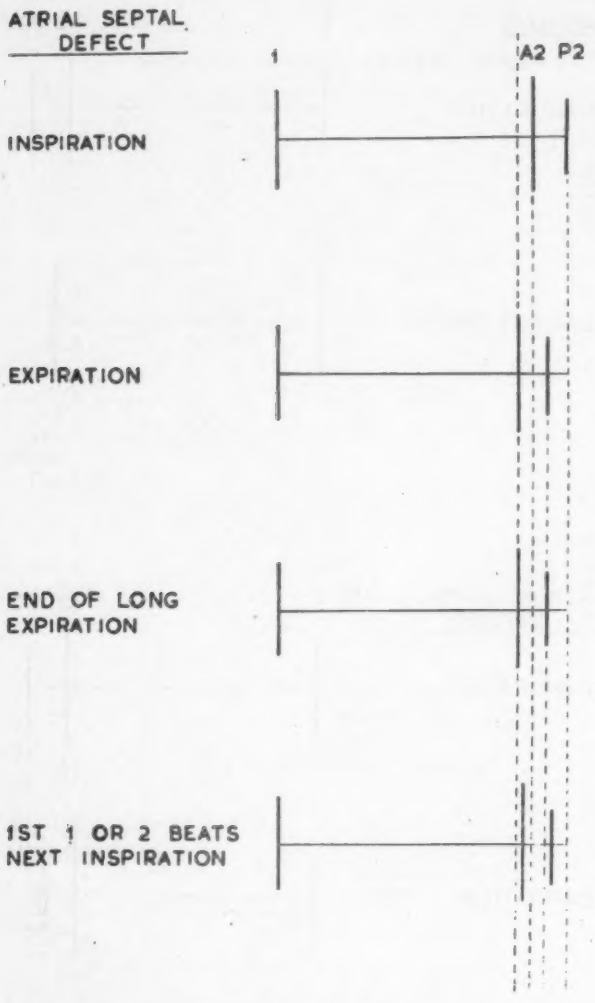


FIG. 4. Diagram representing the relative position of the heart sounds in patients with atrial septal defect during inspiration, expiration, at the end of a prolonged expiration and at the beginning of the next inspiration.

inspiration and that this resulted in a diminished venous return to the left side of the heart unless inspiration was prolonged. Later work, however, suggested that normal inspiration actually results in a decrease in the capacity of the vessels of the lung proportional to the degree of inflation of the lung and that passive expiration results in an increase.[16]

The answer to this perplexing problem has been brought to light by Dornhorst and coworkers.[17] They confirmed the previously noted[6,7,15] decrease in systemic arterial pressure during inspiration at moderate rates of respiration. They showed, however, that during a prolonged expiration, after an initial increase, systemic arterial pressure decreased to its level during the previous inspirations or even lower. To explain this phenomenon they postulated a lag between the effect of inspiration on the right and left ventricles. Inspiration results in augmented filling and increased stroke volume of the right side of the heart. Because of the delay of a few seconds in passage of blood through the pulmonary vascular bed, this augmented volume of blood does not reach the left side of the heart until the subsequent expiration. Thus, left ventricular filling increases, stroke volume increases and systemic arterial pressure rises during expiration. As expiration is prolonged, however, left atrial and ventricular filling from the pulmonary veins decreases, stroke volume decreases and systemic arterial pressure falls.

Factors Influencing Position of A_2 and P_2: Our experimental results are entirely in accord with this hypothesis (Fig. 2). During a prolonged expiration, P_2 moves toward the first heart sound and reaches the position of previous expirations or even earlier. A_2 initially moves away from the first heart sound because left ventricular systole is prolonged as the augmented volume of blood ejected from the right ventricle during the preceding inspiration arrives at the left side of the heart. As expiration is prolonged, venous return to the left atrium and ventricle decreases, the duration of left ventricular systole decreases and aortic value closure becomes earlier. The position which A_2 and P_2 assume relative to the first sound at the end of an expiration depends to some degree on the heart rate and the duration of expiration and probably on the degree of peripheral vasomotor tone[17] and state of the myocardium.

With the inspiration immediately following prolonged expiration, P_2 is delayed as right ventricular filling is increased. A_2 continues to move slightly toward the first sound and is not delayed for the next one or two beats until the venous return to the left side of the heart increases.

This hypothesis also accounts for the mechanism of splitting of the second heart sound during held expiration in many individuals which had not previously been explained.[3]

It is clear that just as closure of the pulmonary valve is delayed in inspiration by the augmented right ventricular stroke volume, closure of the aortic valve is delayed in expiration by the augmented left ventricular stroke volume. Since P_2 becomes earlier with expiration, A_2 and P_2 move closer together or are practically superimposed. Contrariwise, P_2 is delayed and

A_2 becomes earlier during inspiration; thus, splitting increases.

When inspiration is prolonged, the augmented volume of blood ejected by the right ventricle reaches the left atrium and ventricle while inspiration is still in progress; as expected, A_2 is then delayed and the degree of splitting decreases.

In the three patients studied, neither complete right bundle branch block nor "idiopathic" wide splitting of the second heart sound interfered with the normal mechanism. Although A_2 and P_2 were more widely separated than in the normal subjects, the direction of movement was the same.

It is not clear why earlier closure of the aortic valve should contribute more than later closure of the pulmonary valve to inspiratory increase in splitting of the second heart sound in some normal adults[4] and in one of our patients with complete right bundle branch block. Previous studies indicate that respiratory variations in atrial and ventricular filling and ejection are more marked on the right side of the heart than on the left.[7,15,18] Furthermore, Moss and Johnson[19] found that an equal stretch resulted in a greater increase in stroke volume of the right ventricle than of the left.

That such a relation between the movement of A_2 and P_2 is not consistent, however, is illustrated by one of our normal subjects. Initially, the maximum respiratory change in $1\text{-}A_2$ was 16 msec.; $1\text{-}P_2$, 12 msec. Maximum changes in $1\text{-}A_2$ and $1\text{-}P_2$ were each 22 msec. when studied a second time on another day. This suggests that depth of respiration may be an important factor.

SPLITTING OF THE SECOND HEART SOUND IN ATRIAL SEPTAL DEFECT

Inspiratory Delay of P_2 and A_2: In patients with atrial septal defect, P_2 is delayed in inspiration as it is in normal subjects. As noted by Boyer and Chisholm[10] A_2, instead of becoming earlier during inspiration as in normal subjects, is usually delayed, though somewhat less than P_2, and occasionally does not move significantly. Therefore, the second heart sound, which is widely split in expiration in most individuals with uncomplicated atrial septal defect, remains widely split in inspiration and the interval between A_2 and P_2 usually increases only slightly (Fig. 3).

This inspiratory delay of both A_2 and P_2 was present in two patients with right to left shunt through the atrial septal defect (Case 4 with pulmonary hypertension and Case 13 with total anomalous pulmonary venous connection to the left innominate vein and an atrial septal defect or patent foramen ovale[20]).

It is likely that P_2 is delayed in individuals with atrial septal defect, as it is in normal subjects, due to increased filling of the right atrium and ventricle from the systemic venous reservoir. The left to right shunt probably interferes very slightly if at all with the augmented filling of the right atrium during inspiration.

Factors in Atrial Septal Defect Influencing Aortic Valve Closure: Our studies indicate that, unlike the situation in normal subjects, closure of the aortic valve does not depend solely on respiratory variations in the volume of blood ejected by the right ventricle and delivered through the lungs to the left atrium. If this were so, the effect of a prolonged expiration and the next inspiration should be the same as in normal subjects. In fact, however, A_2 becomes earlier at the beginning of expiration rather than being initially delayed as it is in normal subjects. With the next inspiration, A_2 and P_2 are delayed simultaneously (Fig. 4) rather than the delay of A_2 lagging one or two beats behind P_2.

Boyer and Chisholm[10] have suggested that right atriocaval respiratory events may be reflected in the left atrium in the presence of atrial septal defect. Thus, the left atrium may tend also to fill from the systemic venous reservoir with inspiration. There may be no actual right to left shunt in the absence of elevated pulmonary resistance or of an unusual situation such as total anomalous pulmonary venous connection, but the left to right shunt may diminish and effectively increase the filling of the left atrium and ventricle. Therefore, closure of the aortic valve is delayed along with closure of the pulmonary valve.

Occasionally, it appears that the respiratory variation in right ventricular ejection has a relatively more significant influence on filling of the left atrium than the direct influence of respiration on the left atrium in patients with atrial septal defects. The maximum delay of A_2 in such patients (for example, Cases 14 and 15, Table II) occurs during the latter part of inspiration (or if the respiratory rate is fast, even early in expiration) when the augmented volume of blood arriving from the lungs reaches the left atrium and ventricle. It may be that such patients have very small atrial septal de-

fects, but we have no direct information to support this hypothesis. Case 14 had a small left to right shunt (relative to systemic blood flow), but Case 15 had a moderate shunt within the range estimated at cardiac catheterization in most of the other patients.

Effect of Inspiration Following Prolonged Expiration: It is still possible to separate these patients from normal subjects by the response of A_2 in the first one or two beats during an inspiration immediately following a prolonged expiration. The prolonged expiration eliminates the cyclic respiratory variation of blood arriving at the left atrium from the lungs and allows the lesser direct inspiratory effect of augmenting left atrial filling to become apparent. As illustrated in Figure 4, A_2 delays together with P_2 rather than lagging one or two beats behind P_2 as it does in normal subjects (Fig. 2).

The value of this maneuver is illustrated by the results in the patient with anomalous connection of the right pulmonary veins to the right atrium and probably intact atrial septum. During normal respiration, 1-A_2 and 1-P_2 changed very little. With the first two beats during inspiration following a prolonged expiration, P_2 became later but A_2 did not. This is unlike the response of patients with atrial septal defect and is consistent with the diagnosis of an intact atrial septum.

It remains to explain the apparently normal movement of A_2 in Case 16 (Table II). Unfortunately, it was not possible to study the response to prolonged expiration and the following inspiration. One can speculate on the chance that the catheter actually passed through a patent foramen ovale in this patient and that the entire left to right shunt was from the right pulmonary veins anomalously draining into the superior vena cava. Blood samples obtained from the venae cavae and right atrium also suggest this possibility. On the other hand, it may be that there can exist an atrial septal defect large enough to allow the passage of a cardiac catheter but too small to allow respiratory effects on the right atriocaval system to be manifested in the left atrium.

The normal movement of A_2 in this patient and in the three patients with ventricular septal defect and large pulmonary blood flow is important to recognize in either case. This is contrary to the speculation by Boyer and Chisholm[10] that the engorged pulmonary vascular bed fails to respond to respiratory changes and accounts for lack of movement of A_2 during respiration.

Importance of Differential Diagnosis: If the hypothesis that a defect in the atrial septum allows respiratory variations in right atriocaval events to be reflected in the left atrium is correct, it will be very helpful to diagnosis in some patients to measure carefully the movement of the aortic valve closure sound relative to the first heart sound and pulmonary valve closure sound. Thus, it may be possible to detect patients whose physical findings simulate those of atrial septal defect (especially wide splitting of the second heart sound), for example, patients with mild pulmonary valve stenosis, anomalous pulmonary venous connection to the right atrium with intact atrial septum, and abnormally wide splitting of the second heart sound in expiration without obvious cause. Furthermore, it may be possible to detect without cardiac catheterization whether or not an atrial septal defect has been successfully closed by surgery.

Effect of Closure of Septal Defect: The results of our studies in four patients who had undergone surgical repair of an atrial septal defect give some support to this view. However, only one has had a postoperative cardiac catheterization; in this case, there was no evidence of a residual shunt.

Others[21] have reported that in a few cases the split of the second heart sound remains abnormally wide and "fixed" after closure of an atrial septal defect. All four patients in our group also had abnormally wide expiratory splitting of the second heart sound but in none was the split "fixed." We have found it considerably more difficult to be certain of an increase in the interval between A_2 and P_2 by auscultation when the splitting in expiration is already abnormally wide than when the second sound is single in expiration or just detectably split. It is much easier, for example, to detect an increase in the split from 0.02 second (when it is just audible as a split) to 0.04 second than from 0.04 second to 0.06 second.

Careful measurement to establish the direction of movement of A_2 during normal respiration and occasionally after a prolonged expiration may be very helpful in selected patients. This is not difficult if phonocardiograms from two separate locations on the chest, respirations and a suitable time signal are recorded simultaneously.

Summary and Conclusions

Phonocardiograms have been recorded during normal respiration in a group of normal subjects and patients with either atrial septal defect (ASD), anomalous pulmonary venous connection to the right atrium, ventricular septal defect (VSD) or complete right bundle branch block (RBBB) not in heart failure. The intervals between the first heart sound and the two components of the second heart sound, aortic valve closure (A_2) and pulmonary valve closure (P_2), have been measured with an accuracy of ± 2 msec.

In selected subjects from these groups the effects on these intervals of varying rate or depth of respiration, prolonged expiration and prolonged inspiration have been determined.

In normal subjects and patients with VSD or complete RBBB, both earlier movement of A_2 and later movement of P_2 contribute significantly to the inspiratory increase in splitting of the second heart sound. The magnitude of this increase depends mainly on the depth of inspiration.

P_2 is delayed because with inspiration increased filling of the right atrium and ventricle from the systemic venous reservoir results in an increase in right ventricular stroke volume and a slight prolongation of right ventricular ejection.

A_2 is delayed during the subsequent expiration as this augmented volume of blood ejected by the right ventricle arrives from the lungs at the left atrium and increases left ventricular filling, resulting in an increased stroke volume and a slight prolongation of left ventricular ejection. Thus, A_2 and P_2 move closer together or may become practically simultaneous with expiration.

In patients with atrial septal defect, P_2 is delayed within the range of normal during inspiration. A_2, instead of occurring earlier, is usually delayed, though not so much as P_2. Thus, the interval between A_2 and P_2 increases only slightly with inspiration and the splitting is relatively "fixed." Occasionally, A_2 does not move significantly during respiration or becomes earlier at the beginning of inspiration and then is delayed as inspiration continues.

P_2 is probably delayed by the same mechanism that occurs in normal subjects. Closure of the aortic valve, unlike the situation in normal subjects, is not singularly dependent on respiratory variations in the volume of blood ejected by the right ventricle. In the presence of an atrial septal defect, respiratory variations in right atriocaval events may be reflected in the left atrium and the shunt of blood from left to right atrium may decrease with inspiration. This would result in increased left ventricular filling and delayed A_2.

Careful measurement to establish the direction of movement of A_2 during normal respiration and occasionally during and after prolonged expiration may prove helpful in diagnosis in patients whose physical findings simulate those of patients with atrial septal defect and in determining whether or not surgical closure of an atrial septal defect has been complete.

Acknowledgement

I am grateful to Dr. Aubrey Leatham and Professor A. C. Dornhorst, St. George's Hospital, London, for their valued advice in this study. I am indebted to Mr. J. G. Davies for his technical assistance.

References

1. Potain, P. C. Note sur les dédoublements normaux des bruits du coeur. *Bull. et mém. Soc. méd. hôp. Paris*, 3: 138, 1866.
2. Leatham, A. and Towers, M. Splitting of the second heart sound in health. *Brit. Heart J.*, 13: 575, 1951.
3. Leatham, A. Splitting of the first and second heart sounds. *Lancet*, 2: 607, 1954.
4. Boyer, S. H. and Chisholm, A. W. Physiologic splitting of the second heart sound. *Circulation*, 18: 1010, 1958.
5. Boyer, S. H. and Chisholm, A. W. Quoted by McKusick, V. Cardiovascular Sound in Health and Disease, p. 159. Baltimore, 1958. Williams & Wilkins Co.
6. Shuler, R. H., Ensor, C., Gunning, R. E., Moss, W. G. and Johnson, V. The differential effects of respiration on the left and right ventricles. *Am. J. Physiol.*, 137: 620, 1942.
7. Lauson, H. D., Bloomfield, R. A. and Cournand, A. The influence of the respiration on the circulation in man, with special reference to pressures in the right auricle, right ventricle, femoral artery and peripheral veins. *Am. J. Med.*, 1: 315, 1946.
8. Leatham, A. and Gray, I. Auscultatory and phonocardiographic signs of atrial septal defect. *Brit. Heart J.*, 18: 193, 1956.
9. Leatham, A. Auscultation of the heart. *Lancet*, 2: 703, 757, 1958.
10. Boyer, S. H. and Chisholm, A. W. Second heart sound in atrial septal defect. *Circulation*, 18: 697, 1958.
11. Swan, H. J. C., Burchell, H. B. and Wood, E. H. Differential diagnosis at cardiac catheterization of anomalous pulmonary venous drainage related to atrial septal defects or abnormal venous connections. *Proc. Staff Meet. Mayo Clin.*, 28: 452, 1953.
12. Leatham, A., Sloman, J. G. and Jefferson, K. J.

The diagnosis of small ventricular septal defects. Presented at the meeting of the British Cardiac Society, April 1959.

13. Booth, R. W., Chou, T. C. and Scott, R. C. Electrocardiographic diagnosis of ventricular hypertrophy in the presence of right bundle branch block. *Circulation*, 18: 169, 1958.
14. Brecher, G. A. and Hubay, C. A. Pulmonary blood flow and venous return during spontaneous respiration. *Circulation Res.*, 3: 210, 1955.
15. Williams, A. H. and Gropper, A. L. Interrelationships of cardiac output, blood pressure, and peripheral resistance during normal respiration in normotensive and hypertensive individuals. *Circulation*, 4: 278, 1951.
16. Visscher, M. B. The capacity changes in the pulmonary vascular bed with the respiratory cycle. *Fed. Proc.*, 7: 128, 1948.
17. Dornhorst, A. C., Howard, P. and Leathart, G. L. Respiratory variations in blood pressure. *Circulation*, 6: 553, 1952.
18. Cahoon, D. H., Michael, I. E. and Johnson, V. Respiratory modifications of the cardiac output. *Am. J. Physiol.*, 133: 642, 1941.
19. Moss, W. G. and Johnson, V. Differential effects of stretch upon the stroke volumes of the right and left ventricles. *Am. J. Physiol.*, 139: 52, 1943.
20. Edwards, J. E. and Helmholz, H. F., Jr. A classification of total anomalous pulmonary venous connection based on developmental considerations. *Proc. Staff Meet. Mayo Clin.*, 31: 151, 1956.
21. Swan, H., Kortz, A. B., Davies, D. H. and Blount, S. J., Jr. Atrial septal defect, secundum; an analysis of one hundred patients undergoing open surgical repair. *J. Thoracic Surg.*, 37: 52, 1959.

Problems in the Interpretation of Left Atrial Left Ventricular Mean Diastolic Gradients*

ROBERT S. LITWAK, M.D., WILLIAM H. BERNSTEIN M.D., F.A.C.C. *and* PHILIP SAMET, M.D., F.A.C.C.

Miami Beach, Florida

ATRIOVENTRICULAR VALVE mean diastolic and semilunar valve mean systolic gradients have gained acceptance as physiologic hallmarks in the diagnosis of obstructive lesions of the cardiac valves. Increasing experience with right and left heart catheterization has, however, revealed that the recording of such gradients cannot be equated with the existence of organic valvular or ventricular infundibular stenosis. The data leading to the development of this concept have accumulated over the past decade.[1–14] The published studies have described aortic and pulmonary systolic gradients caused by muscular hypertrophy of the left and right ventricular outflow tracts, respectively. The purpose of this paper is to report two subjects with large mean diastolic left atrial-left ventricular gradients; in both patients the mitral valve abnormalities noted at surgery failed to explain the observed gradients.

CASE REPORTS

CASE 1. E. K., a thirty-seven year old white man, had a heart murmur which was first noted during an Army induction physical examination in 1942. He remained asymptomatic during his three years of Army duty. A murmur was again noted on discharge from the Armed Forces. About three years before admission, exertional dyspnea, frequent palpitations and episodes of lightheadedness (without true syncope) developed. Orthopnea, chest pain, hemoptysis, cough, paroxysmal nocturnal dyspnea and edema were absent. The patient denied any symptoms of rheumatic fever in childhood. The patient was a heavy-set, well developed thirty-seven year old white man who appeared neither acutely nor chronically ill. Cyanosis, clubbing, edema, distended neck veins, hepatomegaly and pulmonary rales were absent.

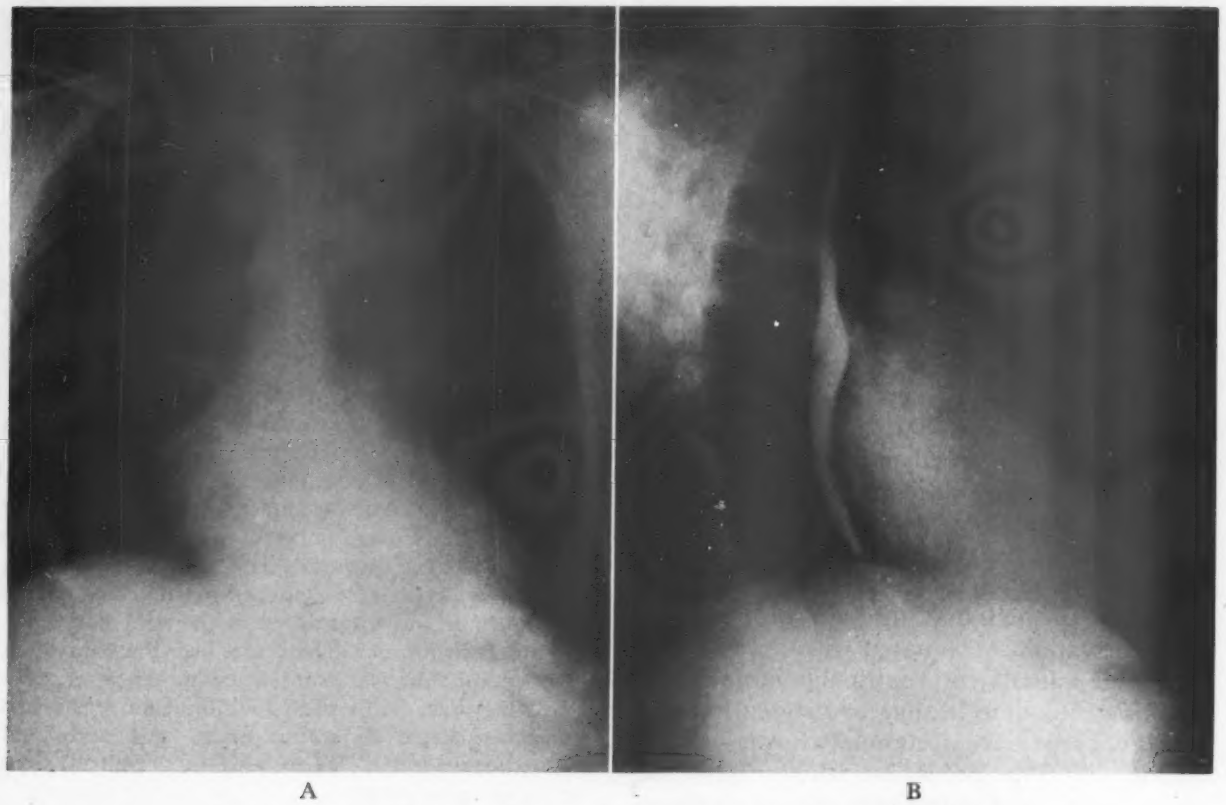
Clinical Findings: Blood pressure was 130/74 mm. Hg, ventricular rate 88 and regular, respiratory rate 15 and temperature normal. Cardiac examination revealed that the palpable maximal impulse was in the left fifth intercostal space outside the midclavicular line. M_1 was louder than M_2 but was not accentuated. P_2 was normal. A_1, P_1 and A_2 were all replaced by murmurs. At the base, a rough grade 4 to 5 systolic, low pitched murmur was heard; this murmur was transmitted to the neck and apex. A grade 1 to 2 diastolic blow was heard maximally at Erb's point, but was transmitted to the apex. No rumbling diastolic or presystolic murmur was heard at the tricuspid or mitral areas. All peripheral pulses were normal. There were no peripheral signs of aortic insufficiency.

On fluoroscopy and x-ray the lungs and pulmonary vessels were normal. The aortic knob was prominent, with minimally increased pulsations. The left atrium and ventricle were 2 plus enlarged. The right heart chambers were also enlarged (Fig. 1). No valvular or aortic calcifications were noted. The electrocardiogram (Fig. 2) revealed left ventricular hypertrophy and atrial enlargement.

Right heart catheterization (in the undigitalized state on May 12, 1958), revealed a minimally elevated pulmonary artery pressure of 29/18, 21 mm. Hg and a normal right ventricular end-diastolic pressure. Right atrial mean pressure was 5 mm. Hg. Pulmonary artery wedge mean pressure averaged 16 mm. Hg. A tricuspid mean diastolic gradient of 5 mm. Hg was present at rest. Cardiac index was minimally reduced to 2.64 L./min./M^2. During steady state exercise, pulmonary artery pressure rose to 36/21, 27 mm.; right ventricular end-diastolic pressure remained normal but right atrial mean pressure rose to 8 mm. Hg and the tricuspid gradient to 8 mm. Hg. Cardiac index changed only slightly during exercise, to 2.79 L./min./M^2. The exercise factor (elevation in blood flow per 100 ml. increase in oxygen consumption) was markedly reduced to 225 cc. (normal 600 to 1,000). Arterial oxygen saturation was normal at rest and during exercise.

Catheterization was repeated after digitalization. Right heart pressures were essentially unchanged.

* From the Department of Surgery and the Section of Cardiology of the Department of Medicine, University of Miami School of Medicine, Coral Gables, Florida, and the Cardio-Pulmonary Laboratory and the Department of Medicine, Mount Sinai Hospital, Miami Beach, Florida.



A B

FIG. 1. Case 1. Teleoroentgenograms. A, P-A view; B, right oblique view.

A significant mean tricuspid diastolic gradient of 5 mm. Hg was again noted at rest (Fig. 3). Pulmonary artery wedge pressure was still elevated to 16 mm. Hg. Cardiac index at rest had fallen 20 per cent to 2.25 L./min./M.^{2}; oxygen consumption at rest fell about 10 per cent. *Left heart catheterization* (Fig. 4) revealed a mean systolic left ventricular-brachial artery gradient of 40 mm. Hg, and a mean diastolic mitral gradient of 10 mm. Hg. There was no evidence of mitral insufficiency on the left atrial curve. The mean left atrial pressure was 15 mm. Hg. The left ventricular end-diastolic pressure was normal (9 mm. Hg).

Operative Findings: These studies led to a diagnosis of physiologically significant tricuspid, mitral and aortic stenosis. Simultaneous correction of all three lesions was projected; the aortic and mitral commissurotomies were planned through a left thoracotomy, the tricuspid through a right thoracotomy incision. Preoperative operating room pressure studies from the left atrium, left ventricle and the internal mammary artery revealed an aortic systolic gradient of 44 mm. Hg, and a mitral diastolic gradient of 10 mm. Hg. The right and left ventricles were "1 plus" and "2 plus" enlarged, respectively. The pulmonary artery was moderately enlarged. A distinct post-stenotic dilatation of the ascending aorta was observed. A thrill was felt over the root of the aorta. On exploration through the left atrial appendage, the mitral valve was found to be only very minimally stenotic with a valve area of over 4.0 sq. cm. The anterior commissure was fused for a length of 3 to 4 mm. and was incised, with a guillotine-type commissurotomy knife, out to the annulus. No fusion was observed at the posterior commissure. Both leaflets were extremely flexible without any palpable evidence of calcification. Subvalvular fusion of the chordae tendineae was absent. Mitral regurgitation was absent before and after the valvular manipulation. The final mitral orifice was estimated at 4.5 to 5.0 sq. cm. The mitral diastolic gradient was still 10 mm. Hg at this point (Fig. 5). Exploration of the left ventricular cavity following the mitral commissurotomy revealed a diffuse subvalvular muscle mass which involved the anterior papillary muscle, a portion of the interventricular septum and the anterolateral aspect of the intracardiac left ventricular wall. The mass was very prominent and lay almost immediately subjacent to the mitral valve. The aortic and tricuspid commissurotomies were performed subsequently. The postoperative course was uncomplicated.

CASE 2. B. H. is a twenty-eight year old white woman. At the age of ten, sore throat, fever and migratory polyarthritis led to a diagnosis of active rheumatic fever. A heart murmur was also noted at this time. Recurrent polyarthritis developed at age fourteen and fifteen. The patient married at age seventeen and delivered a child at age nineteen with-

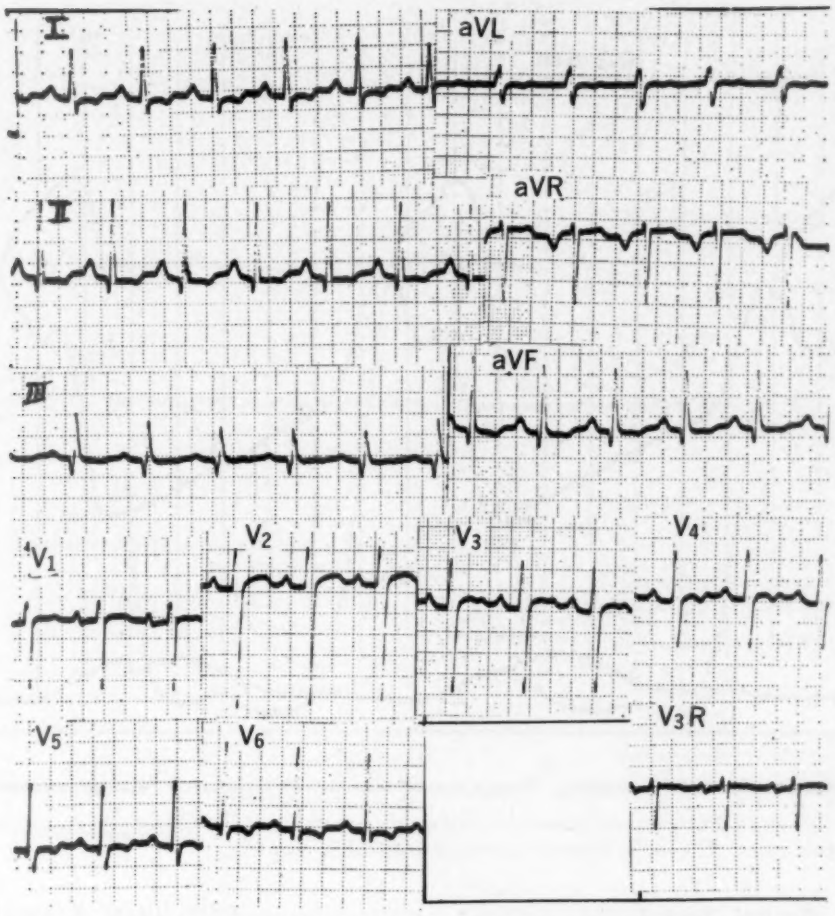


FIG. 2. Case 1. Electrocardiogram. The findings are compatible with left ventricular hypertrophy.

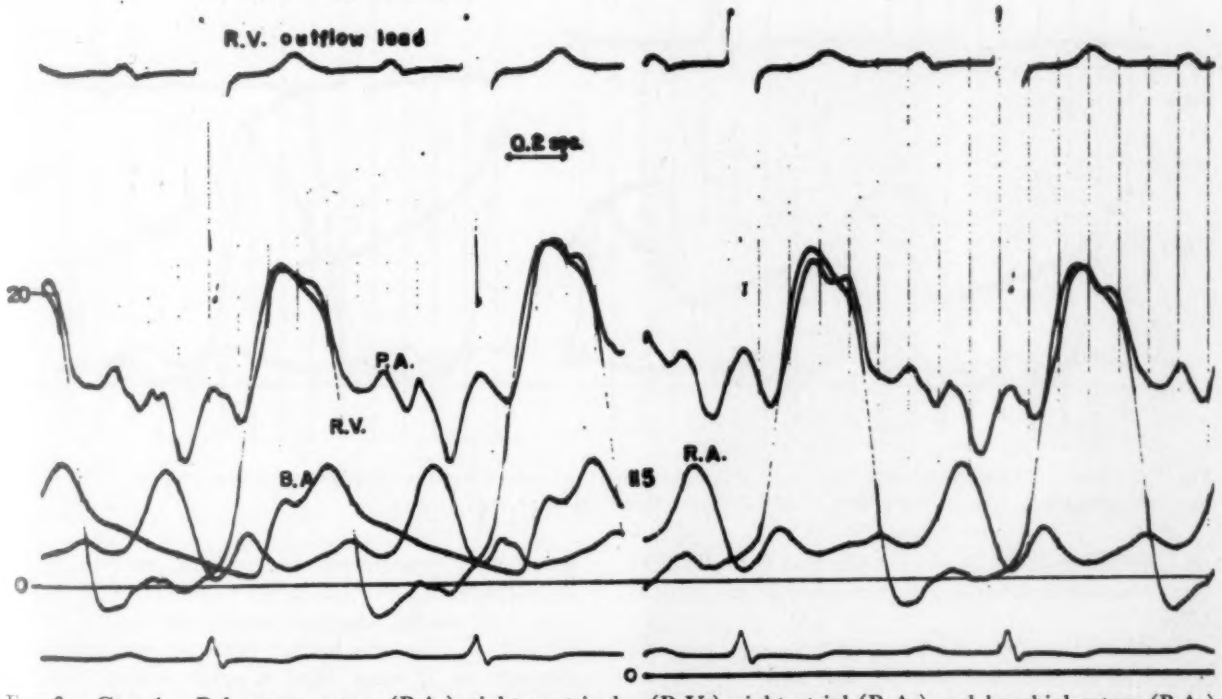


FIG. 3. Case 1. Pulmonary artery (P.A.), right ventricular (R.V.), right atrial (R.A.) and brachial artery (B.A.) curves are recorded simultaneously from the same baseline. The 5 mm. Hg mean diastolic right atrial-right ventricular gradient is readily noted. The right atrial "a" wave is prominent; tricuspid insufficiency is absent.

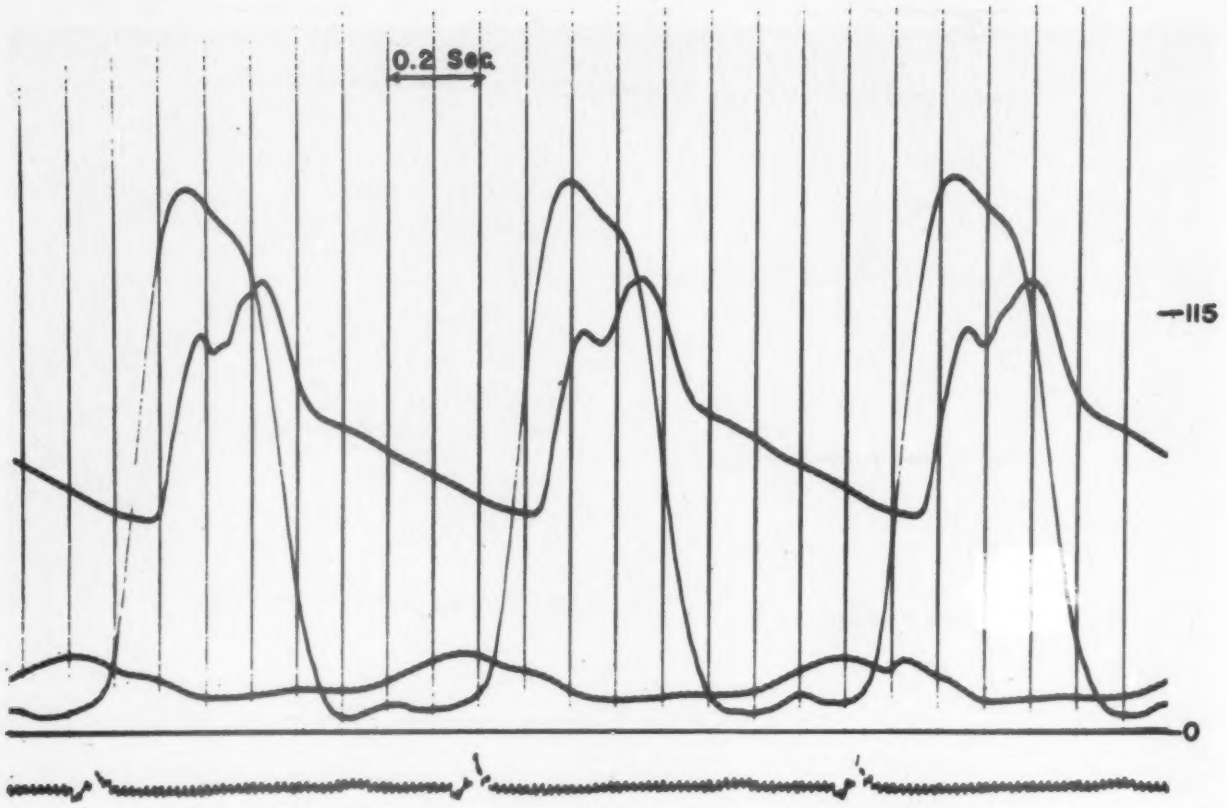


FIG. 4. Case 1. Left atrial, left ventricular and brachial artery curves are recorded from the same baseline and at identical strain gauge sensitivities. The mean diastolic mitral gradient is 10 mm. Hg.

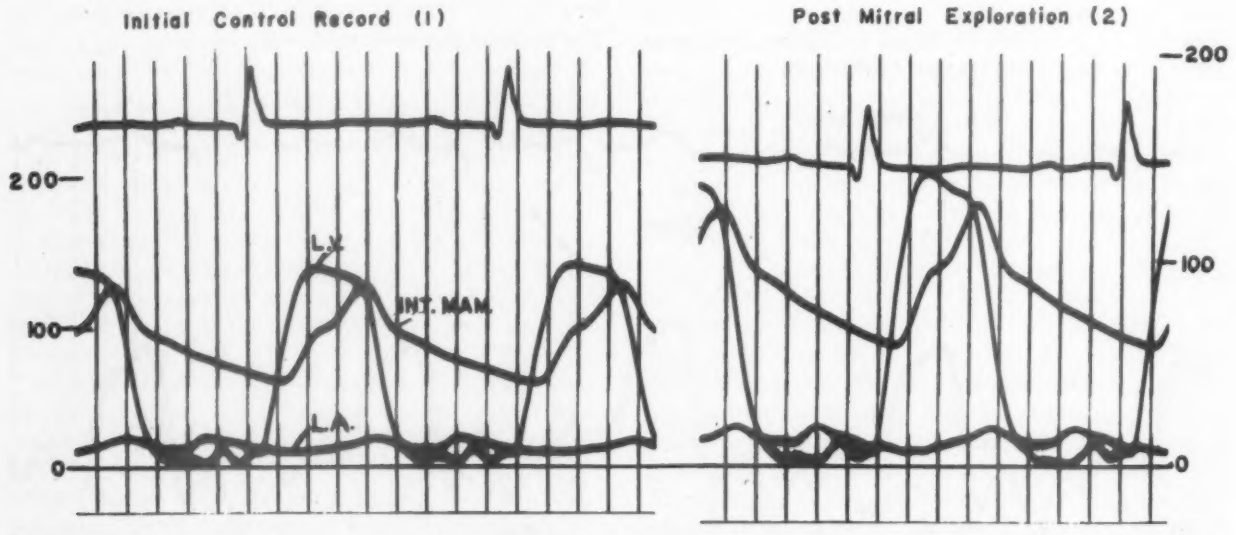


FIG. 5. Case 1. Operating room left atrial, left ventricular and internal mammary artery pressure curves. The mitral diastolic gradient is 10 mm. Hg before and subsequent to mitral valve exploration.

out cardiac decompensation. She was digitalized at age twenty-four because of dyspnea and easy fatigability.

In September 1955 she was seen at another hospital where presystolic and diastolic murmurs were heard together with a soft apical systolic murmur. Right ventricular hypertrophy was noted on fluoroscopy but the electrocardiogram revealed no ventricular hypertrophy. On right heart catheterization at that time, pulmonary artery pressure was normal at rest (26/12, 17) but the wedge pressure was somewhat elevated to 14 mm. Hg. Cardiac index was 3.22 L./min./M^2. During exercise, minimal pulmonary hypertension (30/14, 18) developed. Pulmonary

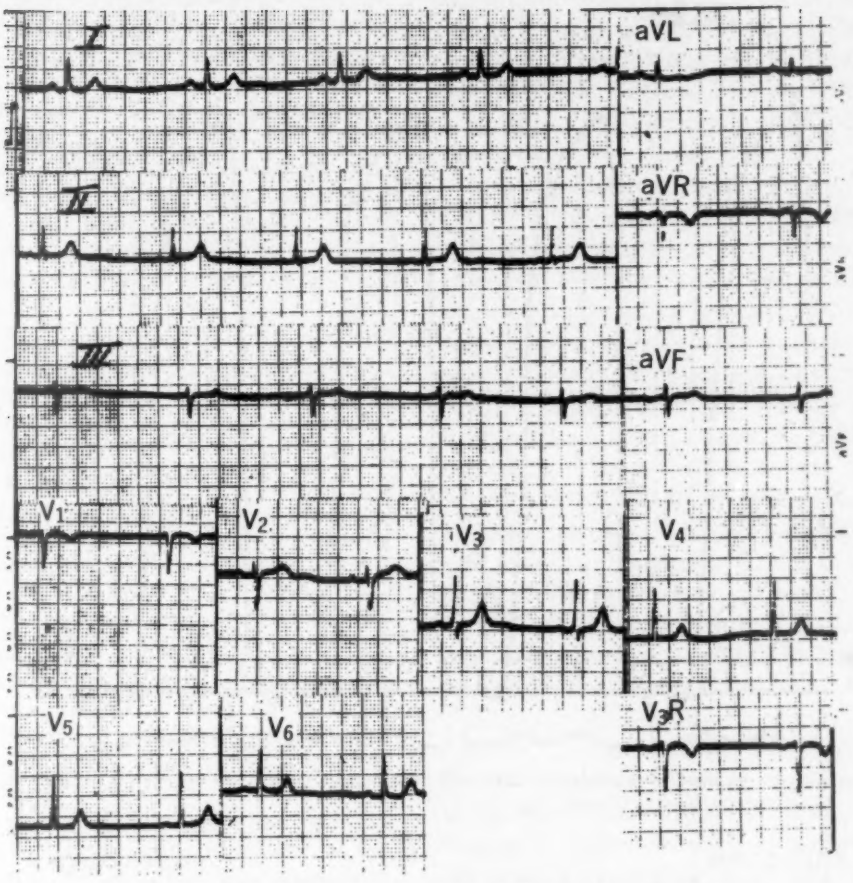


FIG. 6. Case 2. Electrocardiogram. Ventricular hypertrophy is not present.

artery wedge pressure remained unchanged. Cardiac index rose to 4.26 L./min./M²; the exercise factor was 630 ml.

From 1955 to 1959, exertional dyspnea became somewhat worse and appeared on only one to two flights of stairs and during sexual intercourse. Two-pillow orthopnea and paroxysmal nocturnal dyspnea were also noted. She denied cough, hemoptysis and chest pain. Intermittent ankle edema was noted in the premenstrual period. In the three months prior to her admission to Mount Sinai Hospital in 1959, three transient episodes of dizziness, without true syncope, had occurred.

Physical examination revealed a blood pressure of 110/70 mm. Hg, pulse rate of 58 and regular, and a respiratory rate of 15. She was not in acute or chronic distress. No right or left heart failure was evident. The cardiac point of maximum impulse was in the fifth left interspace within the mid-clavicular line. M_1 was louder than M_2 and was accentuated. P_2 was somewhat louder than A_2. A presystolic and diastolic apical rumble and opening snap were heard at the apex; a systolic murmur was absent over this area. A grade 2 systolic murmur was audible at the aortic area, transmitted to the neck.

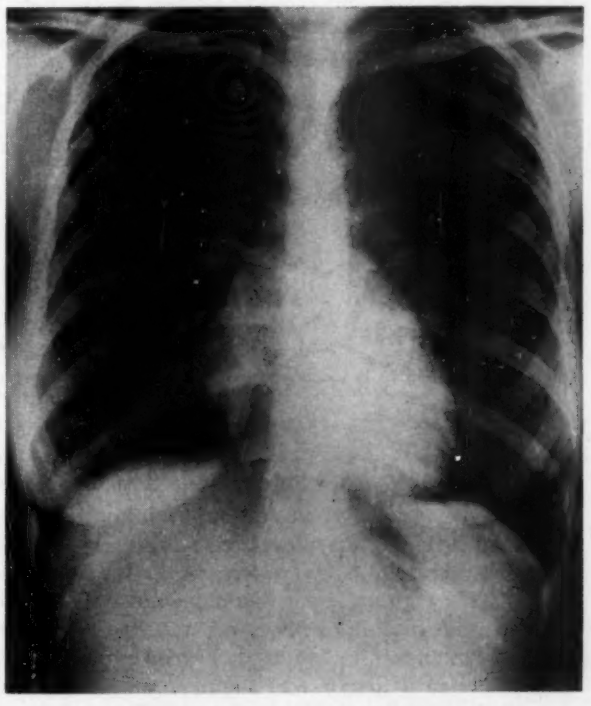


FIG. 7. Case 2. P-A chest film.

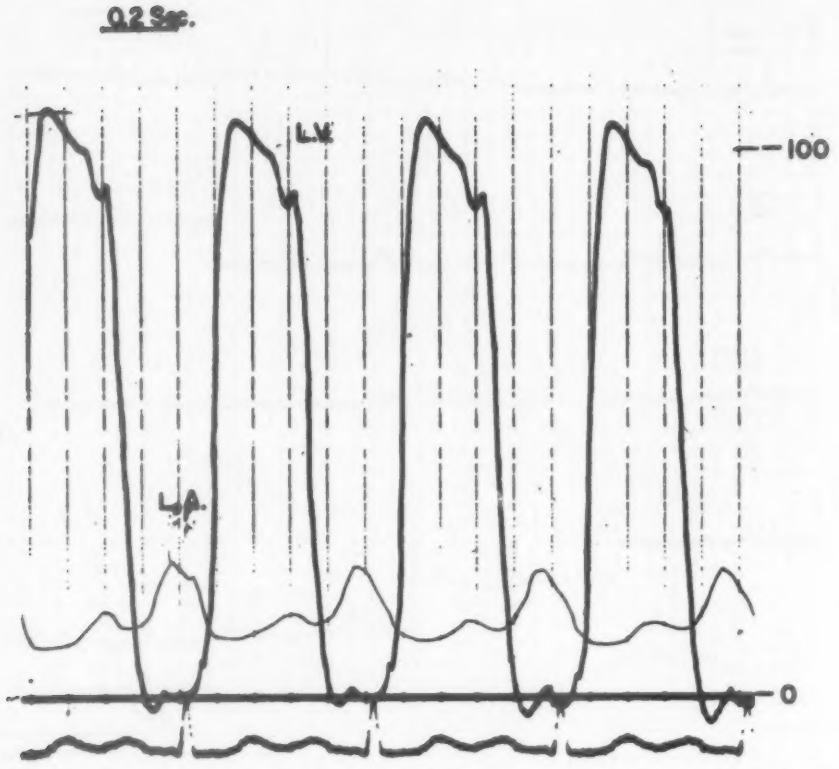


FIG. 8. Case 2. Left atrial and left ventricular pressure curves. The mitral diastolic gradient is 19 mm. Hg.

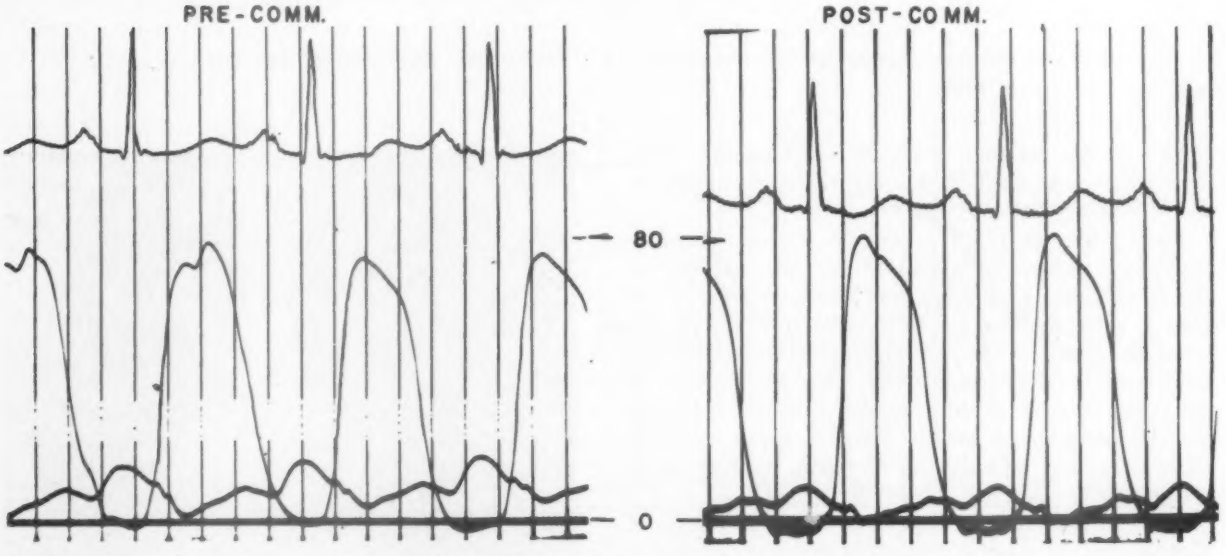


FIG. 9. Case 2. Operating room mitral diastolic gradients. The precommissurotomy gradient is 13 mm. Hg, the postoperative gradient is 9 mm. Hg despite a valve size of 4.5 sq. cm.

The electrocardiogram revealed only minimal P wave abnormalities; ventricular hypertrophy was not observed (Fig. 6). *On fluoroscopy and radiography* (Fig. 7), the transverse cardiac diameter was slightly enlarged. A double contour was noted on the right border of the heart, indicating left atrial enlargement. The pulmonary artery was slightly enlarged. The right atrium and ventricle were 1 to 2 plus enlarged. Posterior displacement of the barium-filled esophagus was evident in the right anterior oblique position. Valvular calcification was not seen. The left ventricle was of normal size.

Right heart catheterization revealed normal pulmonary artery (23/11, 15), right ventricular and right atrial mean pressures. Pulmonary artery wedge pressure was 12 mm. Hg. Cardiac index was normal, 3.32

L./min./M.^{2} Arterial oxygen saturation was 97 per cent. On *left heart catheterization*, left atrial mean pressure was 14 mm. Hg, left ventricular pressure 128/−2, and the mitral diastolic gradient 19 mm. Hg (Fig. 8). No systolic gradient was observed across the aortic valve.

Operative Findings: Mitral commissurotomy was subsequently performed. Preoperative operating room pressures revealed a mitral diastolic gradient of 13 mm. Hg (Fig. 9). Moderate systemic hypotension was present at this time. The right ventricle, left atrium and pulmonary artery were 2 plus enlarged. The left ventricle was not enlarged. A diastolic thrill was palpated over the posterolateral wall of the left ventricle. The mitral valve orifice was approximately 1.0 sq. cm. A large 15 to 18 mm. anterior commissure was initially cut with a guillotine knife; the commissure could then be digitally opened out to the annulus. Virtually no posterior commissural fusion was present. However, a small fibrotic nodule 1 to 2 mm. long was palpated at the point of fusion of the posterior commissural area. No operative manipulation was deemed necessary at the posterior commissural area. The valve leaflets were quite flexible and were not calcified. However, the postoperative mitral diastolic gradient measured 9 mm. Hg (Fig. 9) despite an estimated valve orifice of 4.5 sq. cm. postoperatively. No subvalvular fusion of the chordae tendineae was found but the anterior papillary muscle was markedly enlarged and lay directly subjacent to the anterior commissure of the widely patent mitral orifice. The left ventricular cavity was relatively small in volume. Mitral insufficiency was not present either before or after valvular manipulation.

Right heart catheterization was repeated three months after surgery. Pulmonary artery pressure at rest was 27/12, 15. Right ventricular end-diastolic pressure was 2 mm. Hg. Cardiac index was 3.40 L./min./M^2. During steady state exercise, a slight rise in pulmonary artery pressure (33/16, 19) was noted. Right ventricular exercise pressure measured 33/0. Cardiac index was 4.06 L./min /M^2; the calculated exercise factor equaled 870 ml.

Comments

Functional obstruction to ventricular ejection has been demonstrated repeatedly. Right ventricular-pulmonary artery systolic gradients of varying magnitude are frequently observed in patients with a large left-to-right intracardiac shunt and in subjects in whom ventricular outflow tract work hypertrophy is present. The latter group includes patients with pulmonary hypertension and ventricular septal defect,[9] systemic arterial hypertension,[10] simple pulmonary valvular stenosis[12,13] or idiopathic left ventricular hypertrophy.[8,11,14] The converse problem, i.e., the presence of signs and symptoms of physiologically significant aortic stenosis in the absence of a mean systolic left ventricular-aortic gradient at left heart catheterization, has also been encountered in several laboratories.[15,16]

Functional apical diastolic and presystolic murmurs have been observed. Flint[17] demonstrated that aortic insufficiency could be associated with the murmur of mitral stenosis in patients demonstrated at postmortem examination not to have mitral stenosis. Wykoff and Bunim[18] reported a group of thirteen patients in whom an apical diastolic rumbling murmur was unassociated with atrioventricular valvular disease. Luisada et al.[19] have recently published clinical and physiologic data in a group of thirteen patients "with clinical and phonocardiographic evidence of apical diastolic or presystolic rumbles in whom left heart catheterization failed to prove a gradient across the mitral valve (a minimal gradient was found in one)." These patients exhibited functional apical diastolic murmurs characterized by absent mitral diastolic gradients.

The significance and etiology of the mitral diastolic gradients in the two patients described in this report are difficult to assess. It is our belief that the mitral diastolic gradients recorded in these two patients were mostly caused by hypertrophy of the anterior papillary muscle and the adjacent left ventricular wall, encroaching upon the volume of the left ventricular cavity. Lurie and co-workers[20] have reported several types of obstructive ventricular hypertrophy "wherein a ventricle with a thick, strong wall produces obstruction to blood flow. The three sub-types are: outflow, septal and generalized." Reduced diastolic ventricular volume is described by Lurie—the probable mechanism of the pre- and postoperative mitral diastolic gradient in Case 1, and of the residual postoperative mitral gradient in Case 2. The mitral diastolic gradient in Case 1 is clearly not the result of anatomically significant mitral stenosis. A question may be raised as to the interpretation of the data in Case 2 since organic mitral stenosis was observed at the time of surgery. However, this diastolic gradient largely persisted after complete opening of the valve to 4.5 sq. cm. The absence of subvalvular fusion and valve leaflet calcification, and the presence of flexible valve leaflets in both patients must be emphasized. Under these circumstances, the residual gradients have been ascribed to hypertrophy of the anterior papillary muscle, just as residual right ventricular-pulmonary

artery systolic gradients in simple valvular pulmonary stenosis have been attributed to hypertrophy of the right ventricular outflow tract.

Hypertrophy of the anterior papillary muscle in Case 1 may well be secondary to the aortic valve lesion and the associated left ventricular hypertrophy. If this be the case, the mitral diastolic gradient should be potentially reversible with time at subsequent left heart catheterization. These considerations are not applicable to Case 2 in the absence of an aortic valve lesion. The etiology of the papillary muscle hypertrophy in this patient is obscure. One may speculate, however, as to the role played by the small left ventricle and the diminutive ventricular cavity frequently seen in patients with mitral stenosis in the genesis of the mitral diastolic gradient.

The surgical and autopsy findings in a patient reported by Davis and Andrus[21] raise the possibility of a congenital etiology of the left ventricular muscle mass immediately subjacent to the mitral valve. The necropsy findings in this patient (Case 2)[21] are described as follows: "There was a thin muscle bundle traversing the outflow tract of the left ventricle, attached to the base of the anterior papillary muscle and the septum beneath the aortic valve. At the base of the left ventricle there was a cylindrical bundle of muscle extending from the aortic cusps of the mitral valve along the anterior wall of the ventricle to the septum; there was thinning of the wall of the ventricle at the apex beneath this bundle. The ventricular septum was hypertrophied." "At operation and at autopsy it was apparent that a congenital anomaly of the myocardium of the left ventricle was producing effective stenosis of the ventricle that could not have been surgically corrected."

Teare[22] has presented clinical and postmortem data in a forty-five year old woman who underwent cardiac surgery for mitral "stenosis." At postmortem study localized hypertrophy of the interventricular septum and left ventricular wall was noted; distortion of the mitral valve resulted. The anatomic findings are similar to those in the two patients in this report. Teare has extended these observations to other forms of "obstructive cardiomyopathy."[23]

Summary

Two patients are described in whom the mitral diastolic gradients noted during left heart catheterization were not satisfactorily explained by the anatomic findings observed at cardiac surgery. In one subject aortic and tricuspid stenosis was found at surgery without significant stenosis of the mitral valve. In the second patient a large mitral diastolic gradient persisted after the mitral valve was opened to a size of 4.5 sq. cm. In both instances marked hypertrophy of the anterior papillary muscle in the left ventricular cavity is considered one of the causes of these anomalous mitral diastolic gradients.

References

1. Campbell, M. and Brock, R. C. The results of valvotomy for simple pulmonary stenosis. *Brit. Heart J.*, 17: 229, 1955.
2. Kirklin, J. W., Connolly, D. C., Ellis, F. H., Burchell, H. B., Edwards, J. E. and Wood, E. H. Problems in the diagnosis and surgical treatment of pulmonic stenosis with intact ventricular septum. *Circulation*, 8: 849, 1953.
3. Brock, R. C. Control mechanisms in the outflow tract of the right ventricle in health and disease. *Guy's Hosp. Rep.*, 104: 356, 1955.
4. Brock, R. C. The Anatomy of Congenital Pulmonary Stenosis, p. 114. London, 1957. Cassell & Co.
5. Blount, S. G., Jr., Van Elk, J., Balchum, O. J. and Swan, H. Valvular pulmonary stenosis with intact ventricular septum. Clinical and physiologic response to open valvuloplasty. *Circulation*, 15: 814, 1957.
6. McGoon, D. C. and Kirklin, J. W. Pulmonic stenosis with intact ventricular septum. Treatment utilizing extracorporeal circulation. *Circulation*, 17: 180, 1958.
7. Engle, M. A., Holswade, G. R., Goldberg, H. P., Lukas, D. S. and Glenn, F. Regression after open valvotomy of infundibular stenosis accompanying severe valvular pulmonary stenosis. *Circulation*, 17: 862, 1958.
8. Bercu, B. A., Diettert, G. A., Danforth, W. H., Pund, E. E., Jr., Ahlvin, R. C. and Belliveau, R. R. Pseudoaortic stenosis produced by ventricular hypertrophy. *Am. J. Med.*, 25: 814, 1958.
9. Gasul, B. M., Dillon, R. F., Vrla, V. and Hait, G. Ventricular septal defects. Their natural transformation into those with infundibular stenosis or into the cyanotic or noncyanotic type of tetralogy of Fallot. *J. A. M. A.*, 164: 847, 1957.
10. Brock, R. C. Functional obstruction of the left ventricle. (Acquired aortic subvalvular stenosis.) *Guy's Hosp. Rep.*, 106: 221, 1957.
11. Morrow, A. G. and Braunwald, E. Functional aortic stenosis. A malformation characterized by resistance to left ventricular outflow without anatomic obstruction. *Circulation*, 20: 181, 1959.
12. Campbell, M. Valvotomy as a curative operation for simple pulmonary stenosis. *Brit. Heart J.*, 21: 415, 1959.
13. Johnson, A. M. Hypertrophic infundibular stenosis complicating simple pulmonary valve stenosis. *Brit. Heart J.*, 21: 429, 1959.
14. Brent, L. B., Fisher, D. L. and Taylor, W. J.

Familial muscular aortic stenosis. *Circulation*, 20: 676, 1959.

15. Hancock, E. W., Madison, W. M., Proctor, M. H., Abelmann, W. H. and Starkey, G. W. B. Aortic stenosis of no physiologic significance. *New England J. Med.*, 258: 305, 1958.
16. Samet, P., Bernstein, W. H. and Litwak, R. S. Unpublished observations.
17. Flint, A. On cardiac murmurs. *Am. J. M. Sc.*, 44: 29, 1862.
18. Wykoff, J. and Bunim, J. Observations on an apical diastolic murmur unassociated with valvular disease heard in cases of right ventricular hypertrophy. *Tr. A. Am. Physicians*, 50: 280, 1935.
19. Luisada, A. A., Szatkowski, J., Testelli, M. R. and Prieto, J. B. Apical diastolic and presystolic murmurs of proved functional nature. *Am. J. Cardiol.*, 4: 501, 1959.
20. Lurie, P. R., Shumacker, H. B., Jr., Schulz, D. D., Klatte, E. C. and Grajo, M. Z. Obstructive ventricular hypertrophy in congenital heart disease: definition, classification, and surgical importance. *Circulation*, 20: 732, 1959.
21. Davis, F. W., Jr. and Andrus, E. C. Mitral stenosis in facsimile. *New England J. Med.*, 251: 297, 1954.
22. Teare, D. Asymmetrical hypertrophy of the heart in young adults. *Brit. Heart J.*, 20: 1, 1958.
23. Hollman, A., Goodwin, J. F., Teare, D. and Renwick, J. W. A family with obstructive cardiomyopathy (asymmetrical hypertrophy). *Brit. Heart J.*, 22: 449, 1960.

The "Silent" Lung in Biventricular Congestive Heart Failure

Demonstration of the Syndrome Using the Hepatojugular Reflux and the Circulation Time*

MILES J. SCHWARTZ, M.D.

New York, New York

IT IS well established that physical examination of the lungs is often within normal limits in the presence of significant left ventricular failure[1]. When combined heart failure develops as a result of left ventricular disease, râles are heard at the pulmonary bases.[2] Study of patients undergoing treatment for biventricular congestive heart failure has demonstrated that at an incomplete stage of recovery, in the presence of continued right ventricular insufficiency, overt physical evidence of heart failure, particularly rales, may be absent.

Despite regression of major distress, such patients may complain of vague dyspnea and fatigue. These symptoms often are mild and can be elicited only by careful questioning and observation. Failure to heed the complaints and excessive reliance on gross physical findings, such as rales and peripheral edema, may lead the physician to believe that the patient has been adequately treated. Actually, a significant degree of congestive heart failure may be present and, if so, further therapeutic measures are required.

The purpose of this report is to emphasize and explain the "silent" lung in combined congestive failure, and to indicate the simple diagnostic measures useful in the demonstration of this syndrome.

METHODS

1. The hepatojugular reflux is a clinical phenomenon which establishes the presence of right ventricular insufficiency.[3,4] Hitzig[3] and Burch[5] have provided excellent discussions of the pathophysiology of this phenomenon. A detailed method of eliciting the sign by using the method of Hitzig[3] is included in view of the relative lack of familiarity with the test.

The patient is placed in supine position with the head turned slightly. He is instructed to relax and to breathe regularly and deeply. Gradually increasing pressure over the right upper part of the abdomen is applied for one minute with the palmar surface of the right hand. Simultaneously, the superficial veins in the neck are observed and palpated. The hepatojugular reflux is considered to be present if the superficial cervical veins become visibly fuller or palpably more tense. When any doubt exists, the procedure should be performed and the venous pressure measured by using a manometer placed in an antecubital vein.

In a study of 670 normal individuals Hitzig[3] has noted that one minute of sustained compression of the upper right quadrant produced a decrease in venous pressure ranging from 0.5 to 2.5 cm. H_2O below the initial level in 87 per cent of cases; the remaining 13 per cent remained stable. Thus, use of a manometer provides a precise observation with a definite end-point. Any sustained increase in pressure is considered a positive test.

2. Arm to tongue circulation times were obtained in the usual fashion, using Decholin®,[6] and fluorescein.[7]

CASE REPORTS

The case reports presented are selected to demonstrate the various facets of the syndrome under discussion and are representative of a group of similarly observed patients.

CASE 1. A sixty-four year old white woman was hospitalized for the sixth time on July 13, 1959. She was previously treated for mild diabetes, arterial hypertension, acute myocardial infarction and recurrent left ventricular failure with pulmonary

* From the Department of Medicine, St. Luke's Hospital, New York, New York

edema. During the previous month the patient again became increasingly dyspneic and ankle edema appeared.

Physical examination on admission revealed the patient to be dyspneic at rest and orthopneic. Her weight was 117 pounds. The blood pressure was 110/70 mm. Hg and the pulse was regular at 120. The neck veins were distended and filled from above and below. The apex of the left border of cardiac dullness was percussed at the sixth intercosal space, anterior axillary line. The second pulmonic sound was accentuated and greater than the second aortic sound. A protodiastolic gallop was heard as well as a grade 3, blowing, apical systolic murmur. Rales were heard throughout the entire right lung field and over the lower half of the left posterior lung field. The edge of the liver was palpated 7 cm. below the right costal margin and was tender. There was mild pitting edema in the pretibial and sacral regions. Signs of fluid were apparent at the base of the right lung on the day following admission.

The electrocardiogram taken on the day of admission revealed the rhythm to be sinus tachycardia. Comparison with previous electrocardiograms suggested the possibility of posterior wall myocardial infarction in addition to the old anterior wall infarct. Serial tracings, however, were unchanged.

Hospital Course and Treatment: The patient was treated with bed rest, increments of digoxin, a low salt diet and meralluride. By the fifth hospital day, the edema had disappeared. Roentgenograms of the chest, which were taken on the seventh hospital day, revealed a grossly enlarged heart with congestion of both lung fields and blunting of the left and right costophrenic angles. The signs of effusion, venous distention and gallop slowly disappeared. The lungs became clear of rales on the eighteenth hospital day. At this time, the patient's weight was stable at 104 pounds. The total weight loss was 13 pounds. She was asymptomatic and considered ready for ambulation.

Examination of the chest, on the nineteenth hospital day, revealed the breath sounds to be normal; no rales were heard, even after coughing. The edge of the liver was palpated 5 cm. below the right costal margin and was no longer tender. The hepatojugular reflux was easily elicited and strikingly positive. Circulation time was 35 seconds. It was apparent that biventricular heart failure was still present. Accordingly, bed rest was continued and a diuretic regimen consisting of acetazolamide, ammonium chloride and meralluride was started. A diuresis of 10 pounds took place during the twenty-fifth to the twenty-eighth hospital days. The liver was no longer palpable and the hepatojugular reflux could not be elicited. The circulation time was 29 seconds. Roentgenograms of the chest showed the lung fields to be clear with resorption of the fluid on the left and slight blunting of the costophrenic angle on the right. The size of the heart was unchanged.

The patient was ambulated slowly. During this period her weight remained stable, and the circulation time decreased to 23 seconds. She remained in a state of cardiac compensation and was treated with a low salt diet, digoxin and tolbutamide after discharge. She died suddenly at home on November 4, 1959. Permission for autopsy was not obtained.

CASE 2. A forty-three year old white man was hospitalized for the fifth time on July 3, 1959. He had suffered from angina pectoris after an anterior wall myocardial infarction in 1955. Six weeks prior to admission he noted the onset of dyspnea on exertion. Despite therapy with digitalis and diuretics, the dyspnea increased in severity and orthopnea developed.

Physical examination on admission revealed an acutely ill, dyspneic white man whose pulse rate was 130. The blood pressure was 104/80 mm. Hg. Rales were heard at the base of the left lung and over the lower half of the right posterior lung field. The point of maximal impulse of the heart was 2 cm. beyond the mid-clavicular line in the sixth intercostal space. The second pulmonic sound was greater than the second aortic sound and a diastolic gallop was heard. A slightly tender edge of the liver was palpated 7 cm. below the right costal margin. There was moderate edema of both ankles. The venous pressure was 115 mm. H_2O and the circulation time was 38 seconds. Roentgenograms of the chest revealed bilateral pulmonary edema and cardiomegaly. The electrocardiogram was unchanged from previous records.

Hospital Course and Therapy: The patient responded slowly to a regimen of bed rest, low salt diet, digitoxin and diuretics. The lungs were free of rales by the tenth hospital day. After a loss of 10 pounds, the weight stabilized by the twenty-first hospital day. It was observed that despite the diuresis, the patient remained very apprehensive. He appeared to hyperventilate when seen by the staff. Orthopnea was not noted, but the pulse was rapid and the patient complained of dyspnea when talking or excited although not on exertion. Despite these complaints, only rare and transient rales were heard on repeated examination. Roentgenograms of the chest, on the fortieth hospital day, revealed clearing of the lung fields with persistent cardiomegaly. On the forty-fifth hospital day, the veins of the neck were observed to fill from below. Decholin circulation time on this date was 46 seconds. A repeat study was 43 seconds. A fluorescein circulation time gave a good end-point at 39 seconds.

When examined on the fiftieth hospital day, the total diuresis had reached 13 pounds since admission. A rare rale could be heard in each axilla, but there was no post-tussive rales. A protodiastolic gallop was heard along the left sternal border. The veins of the neck filled slowly from below. A nontender

liver edge was poorly palpated 7 cm. below the right costal margin. The hepatojugular reflux was easily elicited. The venous pressure was 120 mm. of saline.

It was apparent that biventricular heart failure was still present. Digitoxin was discontinued and increments of digoxin were given through the fifty-seventh hospital day at which time the patient reported nausea. No diuresis occurred and the circulation time was 35 seconds. A maintenance dose of digoxin was ordered and a diuretic regimen (acetazolamide, ammonium chloride, chlorothiazide and meralluride) was then instituted. Diuresis of 10 pounds occurred during the next ten days with striking relief of all symptoms. The veins of the neck were flat and, although the second pulmonic sound was still louder than the second aortic sound, the gallop had disappeared. The lungs remained clear. The liver had receded to 3 cm. below the right costal margin and the venous pressure had decreased to 70 mm. of saline. The hepatojugular reflux remained positive while the circulation time and roentgenograms of the chest were unchanged. The response to the Valsalva maneuver[8] was typical of that seen in left and/or right sided heart failure. A continued diuretic regimen of ammonium chloride and meralluride resulted in a weight loss of 5 pounds and a decrease in the circulation time to 25 seconds. The hepatojugular reflux was equivocal at the time of discharge.

Since discharge, the patient has been maintained on a low salt diet and digoxin. He is asymptomatic and the hepatojugular reflux can no longer be elicited.

Comments

Right ventricular insufficiency followed failure of the left ventricle in both of the patients described. Therapeutic measures effected a considerable degree of compensation with disappearance of overt evidence of congestive heart failure. Edema had been resorbed, and the liver was no longer tender although it was still enlarged. It was the elicitation of the hepatojugular reflux which served to demonstrate the previously unsuspected fact that right heart failure was still present. The prolonged circulation times, despite the absence of rales, disclosed the heretofore unrecognized pulmonary congestion[9] which was a reflection of left ventricular failure.

The absence of crepitant rales might be considered perplexing under these conditions. These rales are believed to reflect the presence of fluid in the alveoli and smaller air passages[10] and their continued absence suggests that a significant amount of such fluid was not present. Thus, pulmonary congestion was probably associated with interstitial edema, as emphasized by Parker and Weiss.[11] In the course of a pathologic study of mitral stenosis, these investigators noted that there was prominent interstitial edema in some cases of pulmonary congestion. This was noted particularly in the pericapillary region and often was present without any evidence of intra-alveolar edema. The authors believed that such findings served to explain the absence of rales in certain cases of pulmonary congestion.

The significance of interstitial edema has been well appreciated by radiologists. Evidence of left ventricular failure is often apparent on roentgenograms in the absence of physical findings and occasionally prior to the development of symptoms.[12] Kerley[13] has described fine, dense, horizontal lines at the base of the lungs near the costophrenic angles in cases of mitral stenosis. It is now known that these lines reflect an elevated venous pressure with interstitial edema in the septal regions of the lobules.[14] Identical findings are seen in the course of left ventricular failure. In addition, the hilar clouding and haziness of the lung fields which is seen in left ventricular failure are also believed to reflect the presence of interstitial edema.[14]

Thus, interstitial edema is a recognized entity and is an integral part of the phenomenon of pulmonary congestion. The disappearance of the crepitant rales, however, deserves explanation. It is known[4] that failure of the right ventricle, subsequent to left ventricular failure, often alleviates the symptoms resulting from pulmonary engorgement. This would suggest some alteration in those factors which cause congestion of the pulmonary vascular bed.

Visscher[15] has stated that pulmonary edema is "the consequence of alterations in one or more of four determining variables: (1) membrane permeability, (2) hydrostatic pressures, (3) oncotic pressures, (4) lymph flow rate." He concludes that elevation of the pulmonary capillary pressure (hydrostatic pressure) is probably the most important factor. Thus, it may be suggested that at some critical point in the course of recovery from biventricular failure, pulmonary capillary pressure falls to a level which permits resorption of fluid in the smaller air passages. Although rales would then disappear, considerable interstitial edema and vascular congestion persist and the patient may continue to have symptoms of left ventricular failure.

It is noteworthy that Parker and Weiss[11] could not demonstrate a state of interstitial edema comparable to that seen in mitral stenosis in a group of patients who died as a result of chronic left ventricular failure. However, it has recently been emphasized that the hemodynamic findings in mitral stenosis and chronic left ventricular failure are often comparable in virtually every parameter.[16] In the light of the clinical evidence presented, it appears that further pathologic study of the problem would be of interest.

Matthews and Hampson[17] have written that the hepatojugular reflux fails to be of value when it is most needed, that is, in the detection of cardiac failure in the absence of other evidence. Practical experience, as exemplified in the cases described, would seem to contradict this statement. The observations presented herein demonstrate that the hepatojugular reflux may be positive in the absence of the more common physical finding. It is precisely in these circumstances that it is of greatest value.

The Valsalva maneuver offers additional aid in the diagnosis of occult heart failure.[8] It is to be noted that a positive result may be obtained in right and/or left sided failure. In such circumstances the hepatojugular reflux will aid in determining the presence of right ventricular insufficiency.

The usefulness of the circulation time is established,[18] but the value of serial circulation times has not been sufficiently emphasized. Such studies offer another approach toward evaluating response to therapy, particularly in the patient who cannot be weighed. As a corollary, serial circulation times have been found to be useful in gauging the effectiveness of digitalization when toxicity must be avoided.

Summary

The absence of overt physical findings in certain stages of combined heart failure has been emphasized. The usefulness of the hepatojugular reflux and the circulation time in uncovering the continued presence of congestive heart failure has been stressed.

References

1. Wood, P. Diseases of the Heart and Circulation, 2nd ed., p. 276. Philadelphia, 1956. J. B. Lippincott Co.
2. Friedberg, C. K. Diseases of the Heart, 2nd ed., p. 152. Philadelphia, 1956. W. B. Saunders Co.
3. Hitzig, W. M. Venous pressure curves in normal and abnormal circulatory states. I. Normal venous pressure curves and the negative "hepatojugular phenomenon." *J. Mt. Sinai Hosp.*, 12: 309, 1945.
4. Friedberg, C. K. Diseases of the Heart, 2nd ed., p. 154. Philadelphia, 1956. W. B. Saunders Co.
5. Burch, G. E. and Ray, C. T. Mechanism of the hepatojugular reflux test in congestive heart failure. *Am. Heart J.*, 48: 373, 1954.
6. Gargill, S. L. The use of sodium dehydrocholate as a clinical test of the velocity of blood flow. *New England J. Med.*, 209: 1089, 1933.
7. Lubic, L. G., and Sissman, N. J. A modification of the fluorescein circulation time. *Am. Heart J.*, 44: 443, 1952.
8. Gorlin, R., Knowles, J. H. and Storey, C. F. The Valsalva maneuver as a test of cardiac function. *Am. J. Med.*, 22: 197, 1957.
9. Kopelman, H. The circulation time as a clinical test. *Brit. Heart J.*, 13: 301, 1951.
10. Norris, G. W. and Landis, H. R. M. Diseases of the Chest and Principles of Physical Diagnosis, 5th ed., p. 130. Philadelphia, 1933. W. B. Saunders Co.
11. Parker, F., Jr. and Weiss, S. The nature and significance of structural changes in the lungs in mitral stenosis. *Am. J. Path.*, 12: 573, 1936.
12. Short, D. S. Radiology of the lung in left heart failure. *Brit. Heart J.*, 18: 233, 1956.
13. Kerley, P. Radiology in heart disease. *Brit. M. J.*, 2: 594, 1933.
14. Grainger, R. G. Interstitial pulmonary edema and its radiological diagnosis. A sign of pulmonary venous and capillary hypertension. *Brit. J. Radiol.*, 31: 201, 1958.
15. Visscher, M. B. The genesis of pulmonary edema. *Circulation Res.* 2: 291, 1954.
16. Selzer, A. Hemodynamic sequelae of sustained elevation of left atrial pressure. *Circulation*, 20: 243, 1959.
17. Matthews, M. B. and Hampson, J. Hepatojugular reflux. *Lancet*, 1: 873, 1958.
18. Morris, L. E. and Blumgart, H. L. Velocity of blood flow in health and disease. *Circulation*, 15: 448, 1957

Rebound Hyperlipemia Following Intravenous Heparin*

ASHER WOLDOW, M.D. *and* HERMAN L. WOLF, M.D.

Philadelphia, Pennsylvania

IN MEASURING the degree and duration of alimentary lipemia following a standard fat meal, investigators have shown prolonged and more intense turbidity in patients with coronary artery disease as compared to normal subjects.[1-3] Hahn,[5] in 1943, showed that an injection of a small dose of heparin clarifies lipemic serum. In 1953, it was demonstrated[2,6,8] that when a group of patients with coronary artery disease is given intravenous heparin following a fat load test, the serum shows a significant clearing of lipemia but not quite to the same degree as in the control group.

Since lipemia is generally a gauge of the amount of chylomicrons available and since there is evidence linking large chylomicrons with production of atherosclerosis,[3,4,16] many investigators have been interested in methods of altering lipemic turbidity of serum.

Currently it is considered that there is a lipoprotein lipase[12,14,16] present in the blood which is essential for the conversion of large chylomicrons into smaller, unesterified fatty acids. Heparin[15] is probably an activator of this lipoprotein lipase. Heparin does not clear lipemia in *in vitro* experiments,[2] suggesting that an *in vivo* factor, probably lipoprotein lipase, is necessary for its action.[17] Recently there have been many reports of treatment of the anginal syndrome with repeated doses of heparin given at daily to weekly intervals.

In this present study, we have continued our observations of the clearing effect of heparin on patients with coronary artery disease and normal subjects. We have also carried out experiments in which heparin was given intravenously, immediately following a standard fatty meal, in an attempt to prevent the expected hyperlipemia.

MATERIALS AND METHOD

In the first part of the study, twenty-six patients with unequivocal evidence of coronary artery disease and thirteen normal subjects were used. In this group the effect of a fat load meal on serum lipemia and the effect of heparin on clearing the resultant hyperlipemia was measured. The diagnosis of myocardial infarction was confirmed by the diagnostic pattern in the electrocardiogram in twenty-five of the twenty-six patients used. In the other patient, angina pectoris was severe and an exercise test was found positive. The subjects with myocardial infarction were studied at least four weeks after the acute attack. The age group of those patients with coronary artery disease varied from twenty-eight to seventy-five years, with an average of fifty-seven years. Eight patients were under fifty years of age and six under forty-five years.

The thirteen normal subjects were hospital personnel or other healthy individuals in whom there was no suspicion of atherosclerosis. One subject had a history of liver disease three years previously but his liver function studies were normal except for the thymol turbidity test. The age range of the control group was twenty-five to forty-eight with an average age of thirty-one years. Selection on this basis was done to exclude older age groups in whom evidence of atherosclerosis might be latent.

In the second portion of the study the selection of fourteen patients for premeal heparin injections followed by a fat load test was done on random hospital patients. It was carried out in this way since we were not as interested in comparing disease states as we were in comparing individual responses to the two procedures. In this group the patients were subjected to a routine fat load test as described later. After two or three days the same test was employed, except that the patient was given 50 mg. of heparin intravenously immediately following the fat load meal. In several of the patients the two procedures were reversed in order to exclude the possible effect of experimental bias.

* From the Cardio-Pulmonary Unit and the Department of Radiology of the Albert Einstein Medical Center, Northern Division, Philadelphia, Pennsylvania.

TABLE I
Fat Tolerance Test in Subjects with Coronary Artery Disease

Subject		Optical Turbidity			
No.	Age (yr.) and Sex	Fasting	3 Hour	5 Hour	Postheparin
1	62, M	0.0555	0.1427	0.1249	...
2	73, M	0.0655	0.2291	0.5090	...
3	66, M	0.0802	0.2007	0.4090	...
4	53, M	0.0505	0.5230	0.2924	...
5	60, M	0.0888	0.1905	0.1192	0.0482
6	70, M	0.0555	0.0706	0.1024	0.0757
7	65, F	0.1024	0.1871	0.5850	0.5380
8	48, F	0.0555	0.3190	0.1249	0.0706
9	58, M	0.0505	0.0862	0.1192	0.0605
10	71, M	0.0655	0.2676	0.3970	...
11	74, M	0.0531	0.1805	0.1029	...
12	35, M	0.0835	0.1441	0.1427	...
13	49, F	0.0434	0.2480	0.2147	...
14	64, M	0.0505	0.1079	0.1805	0.0505
15	28, F	0.0706	0.2759	0.2076	0.1299
16	45, M	0.0862	0.3870	0.2840	...
17	40, M	0.0959	0.2676	0.0809	...
18	64, M	0.0555	0.2282	0.2218	0.0505
19	55, M	0.0458	0.1192	0.0809	...
20	32, M	0.0655	0.2364	0.4950	...
21	40, M	0.0706	0.3280	0.2578	...
22	64, F	0.0500	0.1150	0.2000	0.0600
23	63, M	0.0700	0.1000	0.1600	0.1400
24	75, F	0.0200	0.1700	0.0500	0.0450
25	65, F	0.0700	0.2450	0.4400	0.4000
26	63, M	0.0820	0.3420	0.1820	0.0710
Average	57	0.0637	0.2200	0.2241	0.1205

All studies were carried out after a ten hour period of fasting. Following withdrawal of a 10 ml. blood sample into a plain test tube, the subject ate a standard fat meal of 20 per cent sweet cream. The fasting continued and samples of blood were collected at three and five hours. In some of the studies, after removal of the five hour sample, 25 mg. of heparin was injected intravenously and another sample was obtained fifteen minutes later from a vein of the opposite arm.

The blood samples were centrifuged at 3,000 r.p.m. for twenty minutes. The optical density of the serum was measured with a Coleman Jr. spectrophotometer set at a wave length of 650 mμ. The serums were examined for lipemic turbidity (lipemia). This turbidity was used as an index of large chylomicrons as shown by Swank and Wilmont.[7]

RESULTS

Lipemic Turbidity Determinations: Figure 1 graphically presents the average of the lipemic turbidity after fat feeding in all of the twenty-six atherosclerotic subjects. In the normal control series there were thirteen subjects studied for turbidity. Three hours after fat loading the averages for lipemia were significantly higher in the group with coronary artery disease than in the control group. At the end of five hours levels of lipemic turbidity persisted in the group with coronary artery disease while in the control group the levels returned toward fasting.

The results of the individual lipemic turbidity determination for fasting, three hour and five hour samples are shown for each subject in Tables I and II. The predominance of higher levels of optical density in the atherosclerotic subjects is evident although there is some overlapping with the controls. One subject (No. 7, Table I), included in the normal group presented elevated lipemic turbidity. He was known to have had infectious hepatitis two years previously and still had occasional minimal liver tenderness on palpation.

Effects of Intravenous Heparin: Figure 1 also illustrates the influence of intravenous in-

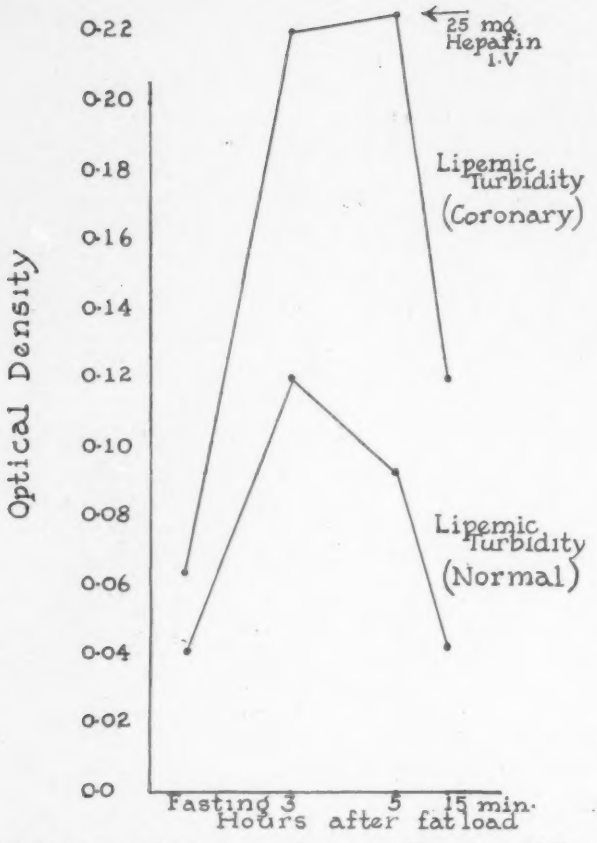


FIG. 1. Fat tolerance test: Averages of lipemic turbidity in twenty-six patients with coronary artery disease and in thirteen control subjects.

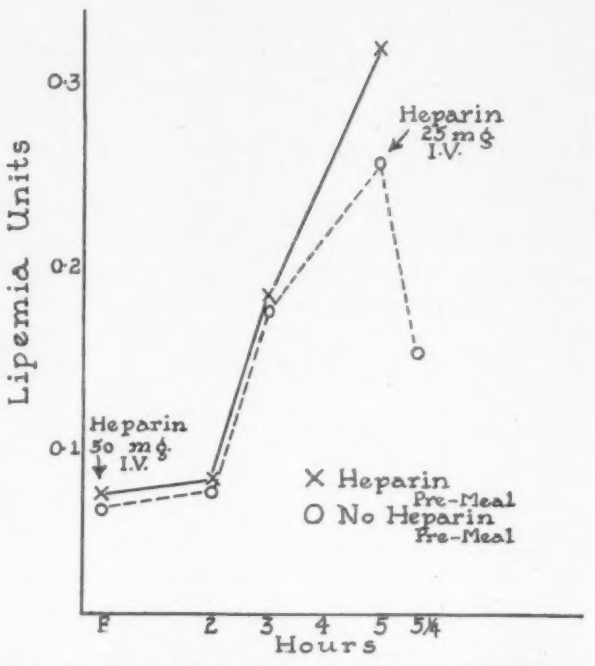


FIG. 2. Comparison of average lipemic turbidity in fourteen subjects given a fat load meal with immediate heparin injection, and with no heparin given until five hours after the meal.

jections of 25 mg. of heparin on lipemic turbidity in fourteen patients with coronary artery disease and five normal subjects. The lipemic turbidity fell to approximately fasting levels in the five normal subjects tested. The reduction in lipemic turbidity from the five hour level was marked in eleven of the fourteen subjects with coronary artery disease and minimal in three.

Fat Tolerance Tests: Figure 2 shows the results of the second portion of experiment when heparin was given immediately after fat loading. Eight of the patients studied had coronary

TABLE II
Fat Tolerance Test in Control Subjects

Subject		Optical Turbidity			
No.	Age (yr.) and Sex	Fasting	3 Hour	5 Hour	Postheparin
1	32, M	0.0223	0.0757	0.1135	...
2	25, M	0.0505	0.1135	0.0505	...
3	26, F	0.0555	0.1549	0.0757	...
4	32, F	0.0458	0.1487	0.0605	...
5	35, F	0.0362	0.0809	0.1024	...
6	48, F	0.0339	0.1871	0.0655	...
7	28, M	0.0458	0.0969	0.2291	0.0355
8	30, M	0.0410	0.4772	0.1549	0.0458
9	27, F	0.0315	0.0605	0.0555	...
10	31, F	0.0434	0.1135	0.0680	...
11	36, M	0.0482	0.1580	0.1192	0.0458
12	26, F	0.0339	0.0835	0.0580	0.0315
13	27, F	0.0458	0.0783	0.0655	0.0410
Average	31	0.0411	0.1177	0.0937	0.0439

artery disease and the other six had various other diseases for which they were hospitalized. We were not as interested in the diagnosis as we were in using each patient as his own control. The average of the fourteen fasting levels in both groups was equal, which is as would be expected. There was no significant difference between the groups at two and three hours after the fatty meal. The significant variation was the unexpected higher level of turbidity at the end of five hours when patients were given heparin in an attempt to prevent hyperlipemia.

Figure 3 graphically shows the degree of change in lipemia from fasting levels in the two studies in the second portion of the experiment. The circles represent the subjects when they were not given premeal heparin and the crosses represent the same subjects when given premeal heparin. The lines between them indicate whether lipemia was greater or less with heparin given immediately after eating. In three of the four cases that can be compared, it will be seen that lipemic turbidity was less after two hours in the patient given heparin immediately after a meal. In three hours there was no significant trend. Eight patients showed more turbidity when not given postmeal heparin, five showed less turbidity and one showed no change.

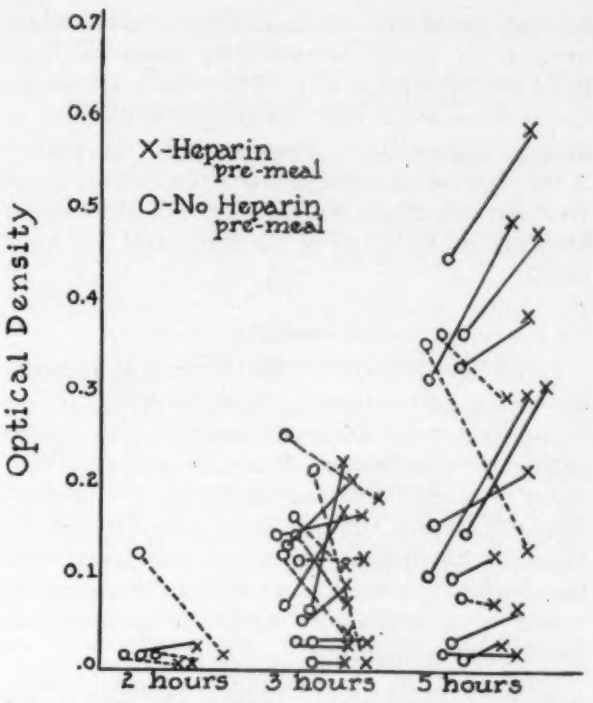


FIG. 3. Optical density measurements of lipemic turbidity after a fat load meal, showing the degree of change from fasting levels at two, three and five hours. The line connecting the two readings for the same subject is solid if turbidity is greater when the subject received heparin immediately following a fat meal. It is broken if turbidity is less when the subject received heparin immediately following the fat meal.

At the five hour level, ten patients who had had heparin immediately after eating showed more turbidity than when not given heparin, two showed less and two showed about the same levels of turbidity.

In Table III we see the absolute values of

TABLE III
Influence of Heparin on Fat Tolerance

Lipemic Turbidity in Subjects Given 50 mg. Heparin 5 Hours after Fat Meal						Lipemic Turbidity in Same Subjects Given 50 mg. Heparin Immediately after Meal			
Case	Fasting	2 Hour	3 Hour	5 Hour	5¼ Hour	Fasting	2 Hour	3 Hour	5 Hour
1	0.050	...	0.115	0.200	0.060	0.055	...	0.225	0.370
2	0.050	...	0.085	0.130	0.050	0.050	...	0.075	0.120
3	0.070	...	0.100	0.167	0.140	0.060	0.110	0.185	0.185
4	0.020	0.035	0.170	0.050	0.045	0.045	...	0.115	0.115
5	0.045	0.055	0.060	0.070	0.080	0.055	0.060	0.070	0.075
6	0.070	0.180	0.245	0.440	0.400	0.095	...	0.210	0.390
7	0.050	0.060	0.175	0.140	0.055	0.045	0.045	0.165	0.165
8	0.045	0.055	0.110	0.360	0.264	0.050	0.070	0.300	0.540
9	0.055	0.100	0.200	0.380	0.520	0.060	...	0.230	0.450
10	0.082	0.215	0.342	0.182	0.071	0.045	0.060	0.235	0.340
11	0.070	...	0.200	0.525	...	0.065	...	0.095	0.660
12	0.050	...	0.110	0.210	0.070	0.050	...	0.140	0.270
13	0.050	...	0.170	0.420	0.160	0.050	...	0.260	0.530
14	0.080	...	0.295	0.440	0.340	0.080	...	0.130	0.210
Average	0.056	0.070	0.169	0.265	0.173	0.057	0.069	0.176	0.316

lipemic turbidity in individual cases when heparin is given immediately after a fatty meal and when it is not. The results are about the same as when only the degree of change, as seen in Figure 3, is demonstrated. In Figure 3 the degree of change from the fasting level was used to eliminate the effect of the fasting level on the turbidity of the three and five hour levels.

Comments

It has been shown[1-3,9] that there is an increase in degree and duration of alimentary lipemia in subjects with atherosclerosis in comparison with normal subjects. Since Swank and Wilmont[7] showed by ultracentrifugation and dark field microscopy that chylomicrons produce the turbidity of lipemic serum, it was considered that turbidity measurements by optical density would be a satisfactory means of quantitating chylomicrons (lipemia).

Subjects with atherosclerosis generally show persistence of lipemia at the fifth hour following a fat meal, while in normal subjects lipemia returns spontaneously toward the fasting level between the third and fifth hours. The injection of heparin at the fifth hour after a fat load meal induces prompt further clearing of the serum to or below the fasting level in the normal subject. This observation suggests that heparin accelerates and intensifies an enzymatic or chemical reaction which is already in progress.[2,5,15] In coronary artery disease it is also apparent that the intravenous injection of heparin clears lipemia following fat loading. Therefore, it would seem that heparin initiates a response at five hours in the group with coronary artery disease which has begun spontaneously at the three hour level in the normal group. Accordingly, it is confirmed that heparin has the "antichylomicronic" action reported by Anderson and Fawcett,[8] and in subjects with atherosclerosis injections of heparin induce more normal handling of alimentary fat loading.[2,10,11]

Along with other investigators,[16] we used heparin in long term therapy to evaluate its effectiveness in preventing angina and myocardial infarction. Heparin in doses of 50 to 100 mg. was injected intramuscularly two to three times a week. In the early period of therapy patients seemed to improve and used less nitroglycerine than usual. However, after several weeks to several months it appeared that there was no longer any significant clinical benefit from long term heparin therapy. The fat tolerance test was repeated on ten patients following three to six months of heparin therapy and showed no essential change from the pretreatment levels of turbidity.

This led to the next phase of this report. Fifty mg. of heparin was given immediately following a fat load meal in an attempt to prevent the expected hyperlipemia. As is seen in the results, the expected did *not* occur. Of the fourteen patients only two had significantly less lipemia after five hours when given heparin immediately following the fat load when compared to their lipemia levels without heparin. It is even more significant that ten patients showed more severe lipemia in five hours when given heparin immediately after eating.

Causes for Rebound Hyperlipemia Following Heparin Injection: These findings suggest two possibilities of heparin action. The injection of heparin may have stimulated the activity of lipoprotein lipase in excess early in the test, exhausting the store of this enzyme; as further fat was absorbed, no more clearing factor was available. Against this theory is the fact that we gave several of the patients second injections of heparin after five hours and good clearing occurred. In this laboratory we are continuing this study of the effect on the fat tolerance test of multiple doses of heparin.

The other possibility of action of rebound hyperlipemia following immediate postmeal heparin injections is that lipoprotein lipase inhibitors or antagonists are activated after the acute clearing stimulated by heparin.[18] This may be part of the reason for the failure of heparin to prevent angina pectoris on a long term basis.

To a small group of four patients we gave heparin two hours following the fatty meal. This was done to show whether rebound hyperlipemia was just the effect of heparin action being completed in the first three hours. In two, the levels of lipemic turbidity were higher after five hours then without heparin while two did not show this. The second two showed five hour levels which were rising and higher than the three hour levels. More studies are necessary to evaluate these findings.

Sublingual Heparin: At this laboratory we have also been using sublingual heparin in an attempt to prevent hyperlipemia, employing the same procedure as for the injectable heparin given immediately postmeal. So far, in the six cases studied we did not see the same pro-

longed clearing observed by Fuller.[4] Five of the six patients in this group also showed an early clearing followed by a later rebound hyperlipemia.

It is apparent, since we have observed acute rebound hyperlipemia following heparin injection, that more studies on the effects of long term heparin therapy on coagulation as well as on lipemia levels are necessary.

Summary

1. Lipemia is more severe in a group of subjects with coronary artery disease than in normal subjects. The degree of difference is accentuated after a fat load test in three and five hour specimens.

2. Heparin, given intravenously, causes a distinct clearing of lipemic turbidity in both groups.

3. Heparin, given intravenously, in an attempt to prevent the expected hyperlipemia following a fat load test, was found to be associated with rebound hyperlipemia.

4. Possible implications of this rebound hyperlipemia are discussed in relation to fat transport.

Acknowledgment

The authors acknowledge with gratitude the technical assistance of Mrs. Margaret Gratz.

References

1. Schwartz, L., Woldow, A. and Dunsmore, R. A. Determination of fat tolerance in patients with myocardial infarction. *J.A.M.A.*, 149:364, 1952.
2. Woldow, A., Chapman, J. E. and Evans, J. M. Fat tolerance in subjects with atherosclerosis: heparin effects upon lipemia, lipoproteins, and gamma globulin. *Am. Heart J.*, 47: 568, 1954.
3. Likoff, W., Berkowitz, D., Woldow, A. and Jacobs, G. Radioactive fat absorption patterns. *Circulation*, 28: 1118, 1958.
4. Fuller, H. Sublingual heparin in hyperlipemia. *Angiology*, 9: 311, 1958.
5. Hahn, P. F. Abolishment of alimentary lipemia following injection of heparin. *Science*, 98: 19, 1943.
6. Weld, C. B. Alimentary lipemia and heparin. *Canad. M. A. J.*, 51: 578, 1944.
7. Swank, R. L. and Wilmont, V. Chylomicra: their composition and their fate after intravenous injection of small amounts of heparin. *Am. J. Physiol.*, 167: 403, 1951.
8. Anderson, N. G. and Fawcett, B. Anti-chylomicronemic substance produced by heparin injection. *Proc. Soc. Exper. Biol. & Med.*, 74: 768, 1950.
9. Jones, H. B., Gofman, J. W., Lindgren, F. T., Lyon, T. P., Graham, D. M. Strisower, B. and Nichols, A. V. Lipoproteins in atherosclerosis. *Am. J. Med.*, 11: 358, 1951.
10. Graham, D. M., Lyon, T. P., Gofman, J. W., Jones, H. B., Yankley, A., Simonton, J. and White, S. Blood lipids and human atherosclerosis. II. The influence of heparin on lipoprotein metabolism. *Circulation*, 4: 666, 1951.
11. Block, W. J., Jr., Mann, F. D. and Barker, N. W. Effect of small doses of heparin in increasing translucence of plasma during alimentary lipemia: studies in normal individuals and patients with atherosclerosis. *Proc. Staff Meet. Mayo Clin.*, 26: 246, 1951.
12. Moreton, J. R. Atherosclerosis and alimentary hyperlipemia. *Science*, 106: 190, 1947.
13. Becker, G. H., Meyer, J. and Necheles, H. Fat absorption and atherosclerosis. *Science*, 110: 529, 1949.
14. Edger, H. A. and Russ, E. M. Composition and distribution of plasma lipoproteins in normal and pathological states. *J. Clin. Invest.*, 31: 626, 1952.
15. Anfinsen, C. B., Boyle, E. and Brown, R. K. The role of heparin in lipoprotein metabolism. *Science*, 115: 583, 1952.
16. Kuo, P. T. and Joyner, C. R. Effect of heparin on lipemia-induced angina pectoris. *J.A.M.A.*, 163: 727, 1957.
17. Korn, E. D. Clearing factor—a heparin activating lipo-protein lipase. *J. Biol. Chem.*, 215: 1, 1955.
18. Day, J. A. and Wilkinson, G. N. Clearing factor inhibitors in human atherosclerosis. *Circulation*, 18: 76, 1958.

The Isometric Period of Contraction as a Determinant of Cardiac Performance and Digitalis Action*

MOHINDER P. SAMBHI, M.B., B.S.†

Dallas, Texas

IT IS generally recognized that the Frank-Straub-Starling principle is not the sole determinant of cardiac response to an increased work-load in the intact animal.[1,2] In addition to neural and humoral factors, the load against which the heart contracts (arterial resistance) has been suggested as an important regulator of cardiac work.[3] The concept of systolic and diastolic loadings of the heart advanced by Cabrera and Monroy[4] attempts to distinguish between the role of the Starling principle and after-loading as mechanisms of compensation to volume and work-load which are simultaneously operative in the intact heart but which may be affected differently in disease. The role of the Starling principle in response to the volume load is apparent but the mechanism of compensation to the after-load remains poorly defined.

Katz[3] has shown that the increase in the work and oxygen consumption of the myocardium is proportional to the after-load. An anticipated effect of such after-load would be to increase the duration of the isometric phase of contraction. In animals Wiggers[5,6] demonstrated that a slight prolongation of the isometric period of contraction accompanied an increase in arterial resistance, while shortening of this period of contraction accompanied any increase in venous return or aortic regurgitation. On the basis of these studies, Wiggers formulated the possible determinants of the phase of isometric contraction to be: (1) arterial resistance, (2) initial tension and length of the muscle fibers, and (3) the gradient of pressure rise during this phase. Katz and Feil[7–9] concluded that in patients with hypertension and aortic stenosis the interval was within the upper limits of normal and was largely independent of the heart rate and the duration of the other phases of the cardiac cycle. However, in these studies, the duration of total systole was estimated from the interval between the first and the second heart sounds, based on an earlier demonstration by Dean and Wiggers[10] that the beginning of the first heart sound marks the point of rise of intraventricular pressure. However, the recent intracardiac catheterization studies of Kelly[11] and Braunwald et al.[12] have shown that the start of the first heart sound marks the closure of the A-V valves and the point at which the rise of intraventricular pressure overtakes the atrial pressure. The location of this point with regard to the start of the initial rise in intraventricular pressure would then be affected by the gradient of the intraventricular pressure on one hand and the factors modifying the venous return and atrial pressure on the other.

Weissler et al.[13] have reported a prolongation of the Q-1 interval in hypertensive subjects. This represents perhaps a delay in closure of the A-V valve which may be due to a less steep gradient of rise in intraventricular pressure. The well recognized lack of correlation between the electrical and the mechanical events of the heart,[14] however, precludes the use of this interval as a direct index of a particular phase of the contraction process. According to Dock,[15] the apex cardiogram may accurately mark the instant when mechanical

* From the Department of Experimental Medicine, The University of Texas Southwestern Medical School, Dallas, Texas. This study was supported by Grants H-4124 of the National Institute of Health and the Grady and Dixie Vaughn Fund.

† Present address: McGill University, Montreal, Canada.

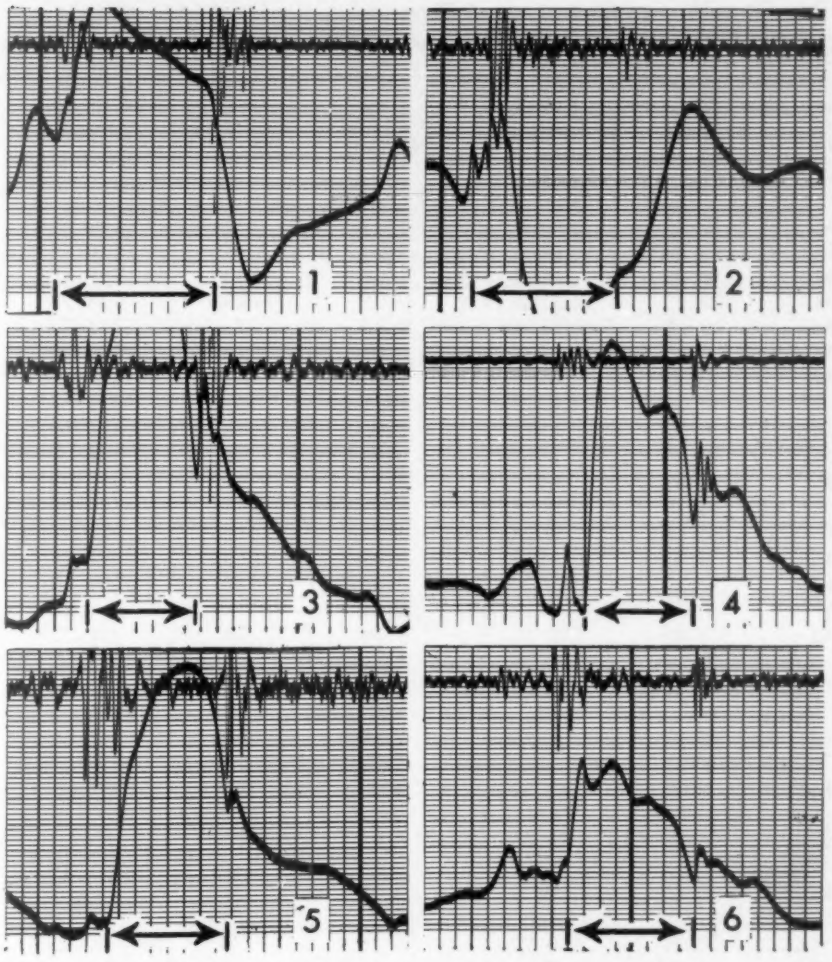


FIG. 1. Representative tracings of the apex cardiogram, arteriogram and heart sounds. (1) Apex cardiogram depicting intraventricular pressure changes; (2) apex cardiogram depicting intraventricular volume changes; (3 and 4) suprasternal aortograms; (5 and 6) subclavian arteriograms. The arrows indicate the duration of total systole in the apex cardiograms and the ejection period in the arteriograms. The difference between these two measurements represents the duration of isometric contraction. Vertical time lines represent 0.02 second.

systole begins. Apex cardiograms were, therefore, utilized in the present study for measurements of the duration of the total systole.

METHODS

Apex cardiograms, central arterial pulse tracings, and the electrocardiographic limb leads were recorded simultaneously with heart sounds on a Sanborn model 62 Twin Beam Cardiette. The heart sounds were recorded with a low frequency pick-up from the third left interspace close to the sternum; the apex cardiograms were recorded with a piezoelectric pick-up through a suction cup attached to the point of maximum impulse, with the subject partially turned to the left side. Patients with a thick chest wall and a poorly palpable or diffuse apex beat were avoided. Suprasternal aortograms and subclavian arteriograms were recorded with the same pick-up except that a straight bell-type attachment replaced the suction cup. The recordings were done at the highest possible sensitivity.

The duration of the total systole was measured from the apex cardiograms as shown in Figure 1. The point marking the start of mechanical activity in the ventricles, which always precedes the beginning of the first heart sound by a small interval, is usually well marked and follows a distinct atrial wave that can be easily identified by its relation to the P wave of the electrocardiogram. The closure of the semilunar valves is also well seen on the apex cardiogram and the vibrations of the second sound coincident with the incisura of the arteriogram aid in its exact localization. The ejection period was measured both from the suprasternal and the subclavian arteriograms, by the distance from the point where the arterial pressure curve rises steeply to the dip of the incisura.

TABLE I
Duration of Isometric Period of Contraction in Normal and Hypertensive Subjects

Case	Age (yr.) and Sex	Total Systole (sec.)	Ejection Period (sec.)	Isometric Period	Heart Rate (per min.)	Blood Pressure (mm. Hg)	ECG Pattern
1	15, M	0.26	0.23	0.03	83	105/68	Normal
2	28, M	0.32	0.26	0.06	78	120/78	Normal
3	44, M	0.28	0.24	0.04	100	130/85	Normal
4	46, M	0.26	0.22	0.04	115	135/90	Normal
5	28, M	0.28	0.24	0.04	72	115/72	Normal
6	33, M	0.35	0.30	0.05	70	118/78	Normal
7	30, M	0.32	0.28	0.04	75	115/70	Normal
8	21, M	0.34	0.29	0.05	65	125/85	Normal
9	39, M	0.32	0.26	0.06	73	120/80	Normal
10	55, M	0.38	0.32	0.06	85	110/70	Normal
11	40, F	0.39	0.29	0.10	67	185/128	No strain*
12	36, M	0.37	0.28	0.09	75	180/100	No strain
13	52, F	0.36	0.24	0.12	89	150/100	No strain
14	63, M	0.42	0.35	0.07	55	160/100	No strain
15	37, M	0.38	0.29	0.09	53	200/120	No strain
16	44, F	0.39	0.29	0.10	60	230/150	No strain
17	51, M	0.42	0.33	0.09	58	190/115	Systolic loading†
18	47, F	0.41	0.29	0.12	60	180/120	Systolic loading
19	60, M	0.39	0.25	0.14	65	200/120	Systolic loading
20	54, M	0.38	0.31	0.07	60	220/120	Systolic loading
21	38, F	0.40	0.34	0.06	62	206/110	Systolic loading
22	41, F	0.40	0.27	0.13	60	200/120	Systolic loading
23	34, M	0.32	0.22	0.10	74	230/150	Systolic loading
24	37, F	0.43	0.34	0.09	52	160/110	Systolic loading
25	61, M	0.44	0.37	0.07	50	180/120	Systolic loading

* No strain: No flattening or inversion of T wave.
† Systolic loading: Inverted T waves in the left precordial leads.

All records were taken at a paper speed of 75 mm. per second; the measurements could be made with the unaided eye, with an accuracy of 0.01 second. Several complexes were measured, but the differences among individual complexes were negligible.

Ten hospitalized subjects with a normal cardiovascular system (based on history, physical examination, chest x-ray and electrocardiogram) served as controls. Fifteen hypertensive patients who were not in cardiac failure and were not taking digitalis were also studied. These included nine patients who exhibited inverted T waves in the left precordial leads of the twelve-lead electrocardiogram; the remaining six patients displayed no evidence of a "strain" pattern. Good tracings before and after digitalization were obtained on five patients with definite signs and symptoms of cardiac failure of varied etiology. In addition, three normal subjects were studied before and after the administration of digitalis. Digitalization was effected by the slow method using digitoxin over a period of three to four days, in all instances except one (Case 4, Table II) in which Cedilanid® was used.

RESULTS

The apex cardiogram has been utilized because of the variable nature of the cardiac impulse and the thickness of the chest wall. Although not a universally applicable and exact method for recording intracardiac mechanical events, the apex cardiogram in those subjects in whom good tracings can be obtained (50 per cent or less) reflects faithfully the pressure changes within the ventricle. Two types

TABLE II
Isometric Period Before and After Digitalization

Case	Age and Sex	Clinical State	Before Digitalis				After Digitalization			
			Heart Rate (per min.)	Total Systole (sec.)	Ejection Period (sec.)	Isometric Period (sec.)	Heart Rate (per min.)	Total Systole (sec.)	Ejection Period (sec.)	Isometric Period (sec.)
1	65, M	Congestive failure	79	0.34	0.28	0.06	100	0.29	0.18	0.11
							60	0.40	0.29	0.11
2	55, F	Left heart failure	75	0.37	0.33	0.04	60	0.38	0.31	0.07
3	68, F	Congestive failure	83	0.38	0.33	0.05	65	0.40	0.31	0.09
4*	58, M	Cor pulmonale	125	0.30	0.24	0.06	115	0.33	0.22	0.11
5	75, F	Congestive failure	83	0.36	0.30	0.06	75	0.38	0.26	0.12
6	22, M	Normal	65	0.34	0.29	0.05	60	0.37	0.27	0.10
7	40, M	Normal	73	0.32	0.26	0.06	72	0.36	0.25	0.11
8	45, M	Normal	85	0.38	0.32	0.06	85	0.39	0.28	0.11

* Rapid digitalization with Cedilanid.

of curves are encountered, as shown in Figure 1 (curves 1 and 2). Curve 1 is the more frequently encountered. Occasionally, one like curve 2, a mirror image of curve 1, is recorded, and is thought to be representative of the volume changes.[16] The fact that in a good tracing the start of the intraventricular pressure or volume change always precedes the beginning of the first sound and follows the atrial wave indicates that the apex cardiogram reflects intraventricular pressure changes as discussed previously A good tracing of the suprasternal aortograms, when obtainable, closely resembles the aortic pulse tracing (Fig. 1, curves 3 and 4). Frequently, however, it is deformed by venous and perhaps intrathoracic pressure changes. In most cases, the subclavian pulse recorded at the suprasternal fossa proved to be satisfactory (Fig. 1, curves 5 and 6). The ejection periods, as measured from the suprasternal aortogram and the subclavian arteriogram, were identical.

It should be emphasized that despite the aforementioned arguments presented, it remains an assumption that the apical and arterial tracings, recorded under the previously mentioned conditions, reflect the events accurately enough to permit computation of the isometric phase of contraction. More convincing evidence of the validity of this assumption might be obtained by cardiac catheterization and simultaneous recording of these events.

Isometric Period of Contraction: As noted in Table I, the duration of this phase is 0.04 to 0.06 second in normal subjects and is distinctly prolonged in those with hypertension (0.07 to 0.14 second). Among the latter, there is no correlation between the length of the isometric phase and the height of the blood pressure and presence or absence of a left ventricular strain pattern in the electrocardiogram. Patients suffering from cardiac failure (Table II) have the same duration of the isometric phase before digitalis as the normal subjects, while after digitalis, both patients in failure and normal persons uniformly display prolongation of this phase.

The data in Table II support the thesis that the cardiac rate has little effect on the duration of the isometric phase. The three normal subjects exhibited a nearly doubled duration of this phase following digitalization without any change in heart rate. This is best illustrated in Case 1 (Table II) in which it was possible to record tracings following digitalization at heart rates of 60 and 100 per minute. The duration of the isometric phase was the same in both instances. It may be surmised that in exercise, shortening of the isometric phase[17] is not due to an increased heart rate. Thus, in Case 6 (Table I), a double two-step exercise test changed the isometric period from 0.05 to 0.02 second, solely by lengthening of the ejection period.

Comments

It seems reasonable to assume that the gradient of rise of intraventricular pressure should be the chief determinant of the duration of the isometric phase of contraction, while the peripheral resistance should determine the height to which the pressure rises. According to Wiggers,[18] this gradient of pressure rise and the duration of the phase are chiefly determined by initial tension and initial length of the ventricular fibers, but "can vary with the inherent contractile power of the cardiac fractions as well." This statement refers to an unknown fundamental mechanism that regulates the gradient of pressure rise in the ventricles. Shortening of the isometric period with a steep rise in the gradient pressure rise may result from changes in the initial state of muscle fibers (increased venous return[19]) or from humoral effects (epinephrine,[20] exercise[17]).

Role of Prolonged Isometric Contraction Phase vs. Gradient of Pressure Rise in Cardiac Contraction: The role of changes in initial tension in relation to the initial length of the muscle fibers is ill-defined. Wiggers[21] has pointed out that in certain clinical situations, the initial length of the fibers rather than tension plays the dominant role. The isometric period of contraction is prolonged in cases of an effective premature beat and in tachycardia (160 to 260 per minute). On the other hand, increased peripheral resistance and digitalization lead to prolongation of the isometric phase. Their effect on the gradient of ventricular pressure rise has not been studied precisely in the intact animal. The conflicting reports based on work on the isolated heart is accounted for by the vitiating effect of increased diastolic volume which occurs in such preparations following a mechanically induced increase in peripheral resistance. The role of neural influences is also obscure. According to Wiggers,[19] the gradient of intraventricular pressure rise remains unaltered in the face of an increase in peripheral resistance, but the isometric period of contraction is somewhat prolonged. In any event, both in case of an increased peripheral resistance and under the effect of digitalis in the intact animal it is the prolongation of the isometric phase of contraction and not the abnormally steep gradient which achieves better contractility and a higher intraventricular pressure. Apparently the two mechanisms work hand in hand. Unless the same effect can be achieved by making the gradient of pressure rise steeper and thus abbreviating the isometric phase (a circumstance governed by the initial length of myocardial fibers and humoral and neural influences), lengthening of the isometric phase is resorted to.

Cardiac failure may be viewed as a situation in which, in spite of the increased diastolic volume, there is failure of the mechanism to achieve better contractility by making the gradient of pressure rise more steeply. Similarly, in tachycardia this mechanism may reach a rate-limiting state. In such situations this mechanism cannot be further stimulated by exercise or epinephrine and prolongation of the isometric phase occurs or may be induced by digitalization.

Prolongation of Isometric Phase and Improved Contractility: How the prolongation of the isometric phase leads to better contractility is questionable. Such a mechanism may be related to the intimate nature of the contractile proteins of the myocardium. Bing[22] has suggested that the phenomenon of "stretch" plays an important role in determining the work performed by the heart. Contractile protein fibers perform more work after stretching. It is conceivable that greater contractility can be achieved either by greater initial length of the fibers or by a longer stretch during the isometric phase of contraction. These two different kinds of stretch may induce in the muscle fibers some physicochemical changes as molecular rearrangement that can also be induced by epinephrine-like substances or digitalis.

Correlation With ECG Changes: Partial evidence only can be presented at present that the duration of the isometric phase determines the pattern of the heart beat that follows. It is of interest to note that the electrocardiographic patterns of the so-called diastolic and systolic loadings of the heart, described by Cabrera and Monroy,[4] can be empirically correlated with a short and long isometric period of contraction, respectively. The conditions leading to prolongation of the isometric phase (digitalis, hypertension, aortic stenosis) sooner or later give rise to negative T waves in the left precordial leads. In this regard, the demonstration by Grant[23] that impaired venous return produced by "head-up tilting" produces S-T wave changes characteristic of full digitalization in partially digitalized subjects, and that these changes can be reversed by rapid intravenous infusions, is significant. Such changes in the repolarization process have been

attributed to the gradient of pressure between the endocardial and the epicardial muscle fibers.[23,24]

In the light of the aforementioned findings, it may be suspected that the duration of the isometric period governs the pattern of contraction and relaxation through differentially affecting the inner and the outer layers of the myocardium. The two types of "stretch" phenomena mentioned earlier may be affecting the inner and the outer layers of the myocardium in a different fashion. Prolongation of the isometric period may lead to better contractility because of the nature of the contractile proteins of the myocardium. There is evidence to suggest[22] that stretch plays an important role in determining the work of the heart since the extracted contractile protein fibers perform more work after being subjected to stretch, and that isometric and isotonic contraction affect two differently reacting contractile proteins.[25] It is thus conceivable that greater contractility may be achieved either by greater initial length or by a longer stretch during the isometric phase of contraction.

Summary

The duration of the isometric period of contraction has been determined from apex cardiograms and arteriograms recorded on thirty subjects. The hypertensive patients showed a significant prolongation of this phase as compared to the normal. This, however, was not related to the height of blood pressure. Digitalization both in normal subjects and patients suffering from cardiac failure produced a uniform and significant increase in the duration of this phase. This increase was unrelated to the cardiac rate.

It is suggested that the prolongation, relative or absolute, of the isometric phase is one of the fundamental mechanisms of cardiac performance in response to an increased work load, and acts in conjunction with the mechanisms responsible for adjustment to volume-load (Starling's principle) by altering the gradient of rise of intraventricular pressure and shortening the isometric phase. This gradient of pressure rise is probably the chief determinant of the duration of the isometric phase of contraction. The mechanism whereby digitalis produces compensation in the failing heart also involves a prolongation of the isometric phase.

Acknowledgment

I wish to acknowledge the inestimable help of Dr. Arthur Grollman, without whose guidance and encouragement this work would not have been possible.

References

1. Grollman, A. The Cardiac Output of Man in Health and Disease. Springfield, Ill., 1932. Charles C Thomas.
2. Stead, E. and Warren, J. Cardiac output in man: an analysis of the mechanisms varying the output based on recent clinical studies. *Arch. Int. Med.*, 80: 237, 1947.
3. Katz, L. N. Analysis of the several factors regulating the performance of the heart. *Physiol. Rev.*, 35: 91, 1955.
4. Cabrera, E. C. and Monroy, J. R. Systolic and diastolic loadings of the heart. *Am. Heart J.*, 43: 661, 1952.
5. Wiggers, C. J. Studies on the consecutive phases of the cardiac cycle. *Am. J. Physiol.*, 56: 439, 1921.
6. Wiggers, C. J. and Maltby, A. B. Further observations on experimental aortic insufficiency. *Am. J. Physiol.*, 97: 689, 1931.
7. Katz, L. N. and Feil, H. S. Clinical observations on the dynamics of ventricular systole. *Arch. Int. Med.*, 32: 672, 1923.
8. Feil, H. S. and Katz, L. N. Clinical observations on dynamics of ventricular systole. *Arch. Int. Med.*, 33: 321, 1924.
9. Katz, L. N. and Feil, H. S. Clinical observations on the dynamics of ventricular systole. *Heart*, 12: 171, 1925–1926.
10. Wiggers, C. J. Studies on the consecutive phases of the cardiac cycle. *Am. J. Physiol.*, 56: 415, 1921.
11. Kelly, J. J. Diagnostic value of phonocardiography in mitral stenosis. *Am. J. Med.*, 19: 862, 1955.
12. Braunwald, E., Moscovitz, H. L., Amram, S. S., Lasser, R. P., Sapin, S. O., Himmelstein, A. and Ravitch, M. M. The hemodynamics of the left side of the heart. *Circulation*, 12: 69, 1955.
13. Weissler, A. M., Leonard, J. J. and Warren, J. V. Observations on the delayed heart sounds in mitral stenosis and hypertension. *Circulation*, 18: 165, 1958.
14. Samet, P., Silverman, L., Bernstein, W. H. and Litwak, R. S. Electrical and mechanical asynchronism in the cardiac cycle. *Am. J. Cardiol.*, 3: 482, 1959.
15. Dock, W. Heart Sounds, Cardiac Pulsations, and Coronary Disease. Lawrence, Kan., 1956. University of Kansas Press.
16. Luisada, A. A. The Heart. Baltimore, 1954. Williams & Wilkins Co.
17. Rushmer, R. F. and West, T. C. Role of autonomic hormones on left ventricular performance continuously analyzed by electronic computers. *Circulation Res.*, 5: 240, 1957.
18. Wiggers, C. J. Pressure Pulses in the Cardiovascular System. New York, 1928. Longman Green & Co.
19. Wiggers, C. J. Circulatory Dynamics. Modern Medical Monographs. New York, 1952. Grune & Stratton.

20. Wiggers, C. J. Studies on the cardiodynamic actions of drugs. *J. Pharmacol. & Exper. Therap.*, 30: 233, 1927.
21. Wiggers, C. J. Physiology in Health and Disease. Philadelphia, 1949. Lea & Febiger.
22. Bing, R. J. Significance of the newer knowledge of contractile proteins for cardiology. In: World Trends in Cardiology, III. Edited by Cain, A. S. New York, 1956. Hoeber-Harper.
23. Grant, R. P. Physiologic aspects of clinical electrocardiography. In: Clinical Physiology. Edited by Grollman, A. New York, 1957. McGraw-Hill.
24. Hecht, H. H. The electrophysiology of the heart. *Ann. New York Acad. Sc.*, 65:932, 1957.
25. Szent-Gyorgyi, A. General views on the chemistry of muscle contraction. *Fortschr. Kardiol.*, 1: 6, 1956.

Experimental Study

QRS Component of the Spatial Vectorcardiogram and of the Spatial Magnitude and Velocity Electrocardiograms of the Normal Dog*

HERMAN K. HELLERSTEIN, M.D. *and* ROBERT HAMLIN, D.V.M.

Cleveland, Ohio Columbus, Ohio

THE purposes of this paper are: (1) to present a systematic study of the QRS component of the spatial vectorcardiogram (QRSsÊ loop) and the spatial magnitude (sM ECG) and spatial velocity (sV ECG) electrocardiograms of the normal dog; (2) to correlate the dog's vectorcardiogram with scalar electrocardiograms; and (3) to demonstrate a possible method of correlating both vectorcardiogram and electrocardiogram with the cross sectional anatomy of the heart and the activation of the interventricular septum and ventricular myocardium.

Despite the recent resurgence of interest in the ventricular activation process of the dog, there has been only one systematic study of the spatial vectorcardiogram of the dog[1] and one study attempting to correlate the sense of the vectorcardiographic loop with the sequence of the activation process of the ventricles.[2] In the present report the use of differentially dissected vectorcardiograms[3] and of two new transformations of the electrical activity of the heart, the spatial magnitude electrocardiogram[4,5] and spatial velocity electrocardiogram, may contribute to the understanding of the ventricular activation process.

MATERIALS AND METHODS

Forty healthy dogs were studied. Their ages ranged between one and seven years. Body weights ranged from 7.5 to 30 kg.

Animals were anesthetized with intravenous pentobarbital sodium (30 mg. per kg. of body weight). Sinus arrhythmia was abolished by intravenous atropine sulfate (0.001 gm. per dog). All animals were studied in right lateral recumbency.

Electrocardiograms were recorded at 75 mm./second paper speed on a Sanborn twinbeam electrocardiograph. Unipolar thoracic electrocardiograms were taken from areas on the horizontal† plane determined by the dorsal spinous process of the seventh thoracic vertebra (Fig. 1).

VECTORCARDIOGRAPHIC STUDIES

Vectorcardiograms were taken on a Dumont type 279 dualbeam oscilloscope in which the beams were interrupted 600 times per second and the images were shaped to show the direction of the sweep. Simultaneous with and adjacent to each vectorcardiographic loop, the scalar electrocardiographic projections, along the Yax is in the frontal and sagittal planes, and along the Z axis in the horizontal plane, were recorded in twenty-eight dogs. In

† For the sake of conformity with human terminology, this plane is called horizontal although it is actually coronal.

* From the Department of Medicine, University Hospitals of Cleveland and the School of Medicine, Western Reserve University, Cleveland, Ohio. Supported in part by grants from The Cleveland Area Heart Society.

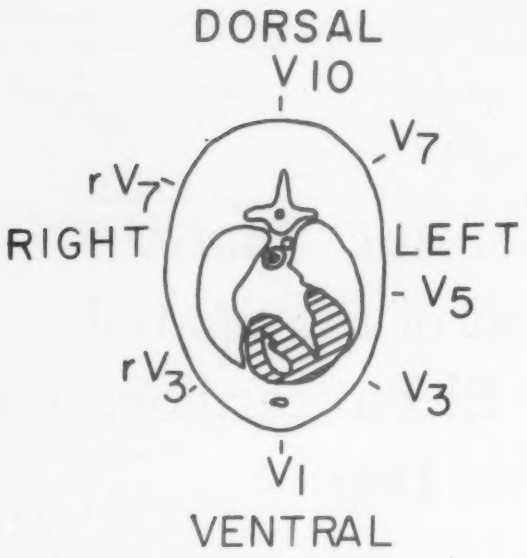


FIG. 1. Designation of unipolar leads in the horizontal (coronal) plane in the normal dog. In lead V_{10} position the exploring electrode is placed on the dorsal spinous process of the seventh thoracic vertebra; in lead V_1 position, on the mid-sternum at the junction of the fourth chondral cartilage. Other electrode placements vary according to the morphology of the thorax but are always placed in the plane determined by lead V_{10} and V_1 positions. In lead V_3 position the left lateral thorax is usually at the level of the olecranon and the apex beat. In lead V_5 position the left lateral angle of the thorax is usually in the fifth intercostal space. In lead V_7 position the left lateral thorax is near the caudal margin of the scapula.

twelve additional dogs, simultaneous frontal and sagittal, and frontal and horizontal loops were recorded. A special electronic apparatus made possible the isolation of only the QRS component of both vectorcardiogram and electrocardiogram.[3] Permanent records were made with a special Dumont Polaroid Land camera and with a standard 35 mm. camera.

The Wilson equilateral-tetrahedral system of electrode placement and correction was used[6,7] with the back point reference electrode placed on the dorsal spinous process of the seventh thoracic vertebra.

The frontal plane is viewed from the dog's ventral surface, the horizontal plane from the anterior (cephalic), and the sagittal plane from the dog's right lateral side. The polarity of the coordinate system for each plane was designated according to the nomenclature of Helm.[8]

The frontal, sagittal and horizontal plane vectorcardiograms of forty dogs were analyzed for general configuration, length-width ratio and direction of inscription. In twenty-eight dogs, the magnitude, direction and time after onset of the QRS were analyzed for each major vector having maximal cephalic, caudal, dorsal and ventral projections. Since the origin and termination of each QRS loop were clearly demonstrated by the technic employed

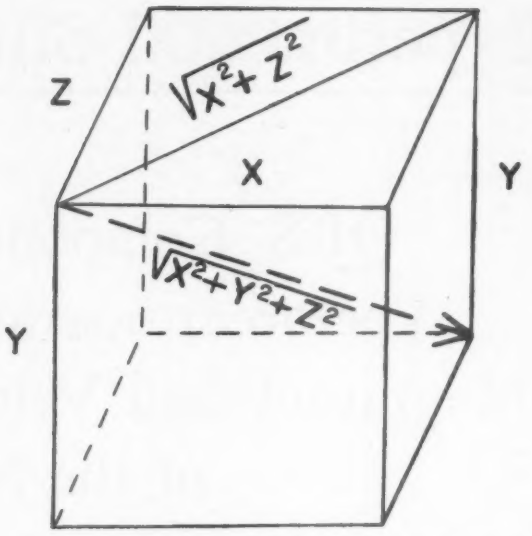


FIG. 2. Derivation of the spatial magnitude (sM) of an instantaneous vector. (See text.)

and were related to the simultaneously recorded QRS complex of the scalar electrocardiogram, the time of the origin, terminus and any other point on the QRS loop could be determined, accurately at least to 1 millisecond.

The durations of the following forces were determined: the total initial cephalic, caudal, terminal cephalic, dorsal and ventral.

SPATIAL MAGNITUDE ELECTROCARDIOGRAM (SM ECG)

The instantaneous spatial magnitude of the "dipole" current-time curve was estimated by inspection in twenty-eight dogs and was computed from simultaneously recorded frontal and sagittal plane projections of the QRSsÊ loops of six dogs. The spatial magnitude (sM) was calculated for the

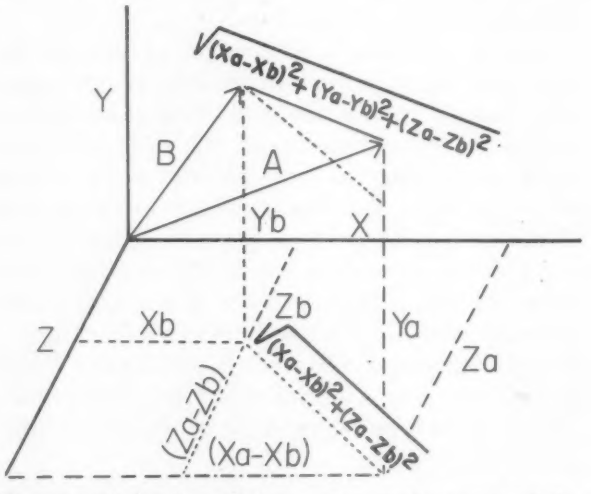


FIG. 3. Derivation of the spatial displacement of the termini of two consecutive vectors A and B. (See text.)

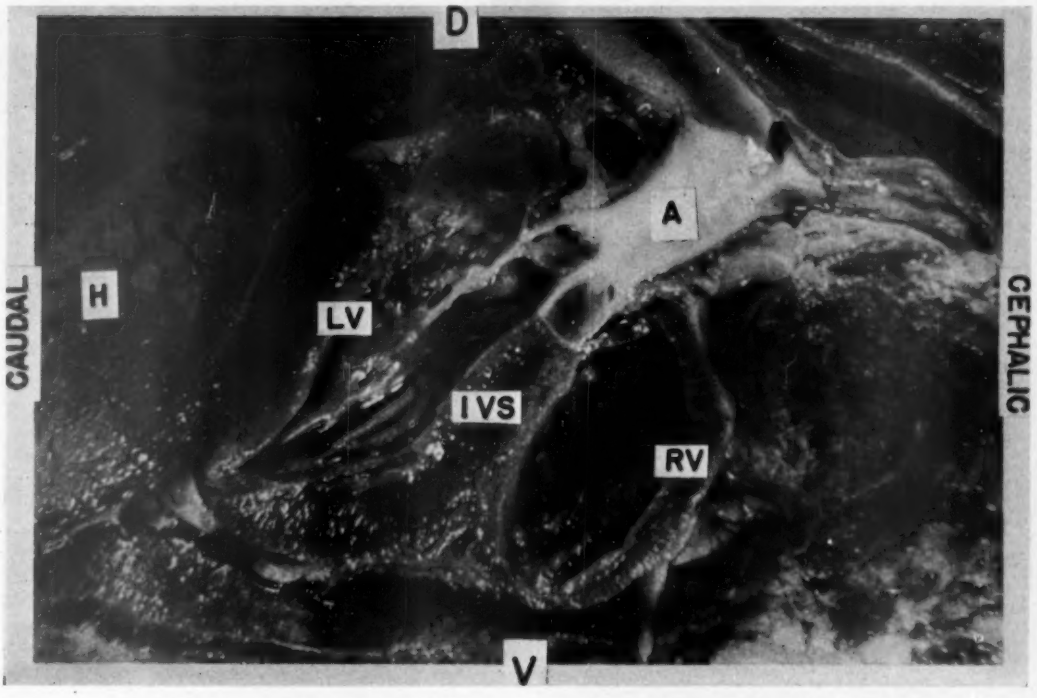


FIG. 4. Anatomic cross section through the median sagittal plane of a normal dog, viewed from the right side. D represents dorsum, V—ventrum, LV—left ventricle, RV—right ventricle, IVS—interventricular septum, A—aorta, H—liver. (See text.)

vector force at each time interruption over the duration of the QRS complex, by measuring the projection of the force along the X, Y and Z axes, squaring each separately, and extracting the square root of their sums (Fig. 2):

$$sM = \sqrt{X^2 + Y^2 + Z^2}$$

The instantaneous spatial magnitudes were then plotted against time.

SPATIAL VELOCITY ELECTROCARDIOGRAM (sV EGG)

The spatial displacement between the termini of consecutive vectors (every 0.06 of a second) was obtained by measuring the projection of the vectors formed by the termini of consecutive vectors on the frontal, sagittal and horizontal planes, summing their squares, and extracting the square root (Fig. 3):

$$sV = \sqrt{(Xa - Xb)^2 + (Ya - Yb)^2 + (Za - Zb)^2}$$

or

$$sV = \sqrt{\left(\frac{dx}{dt}\right)^2 + \left(\frac{dy}{dt}\right)^2 + \left(\frac{dz}{dt}\right)^2}$$

(Xa − Xb), (Ya − Yb) and (Za − Zb) represent ΔX, ΔY and ΔZ, respectively, i.e., the change in X, Y and Z projections in one unit of time. The spatial displacements of the successive instantaneous vectors of the entire QRS complex were then plotted against time, forming the spatial velocity electrocardiogram (sV ECG) of the QRS complex.

The cardiac rhythm and rate and the P, P-Q, Q, R, S, Q-T and R-R intervals were determined from the electrocardiograms which were magnified tenfold by projection. The circumferential thoracic leads were compared with scalar electrocardiograms derived from the horizontal plane vectorcardiograms.

ANATOMIC STUDIES

In nine anesthetized, frozen dogs, lying in right lateral recumbency, anatomic cross sections of the thorax were obtained in the frontal, sagittal and horizontal planes corresponding to similar planes of the vectorcardiogram (Figs. 4, 5 and 6).

Correlation of the anatomic location of various parts of the ventricles was made with portions of the vectorcardiograms representing their activation.

RESULTS

QRSsÊ LOOPS

Configuration: The typical QRSsÊ loop (Fig. 7) determines a heart-shaped area in a plane almost coplanar with the median sagittal plane. The projection of the spatial loop on the sagittal plane results in a heart-shaped area having a length-width ratio of 1.6 : 1, and an inscription always in a clockwise rotation. The projection of the spatial loop on the horizontal plane results in an area shaped as an elongated scalene triangle having an average length-

FIG. 5. Ventral view of an anatomic cross section of a normal dog through a frontal (ventral) plane at the point of the olecranon, approximately one-third of the dorsoventral distance from the sternum. RTL represents right thoracic limb; LTL, left thoracic limb. Other abbreviations as in Figure 4.

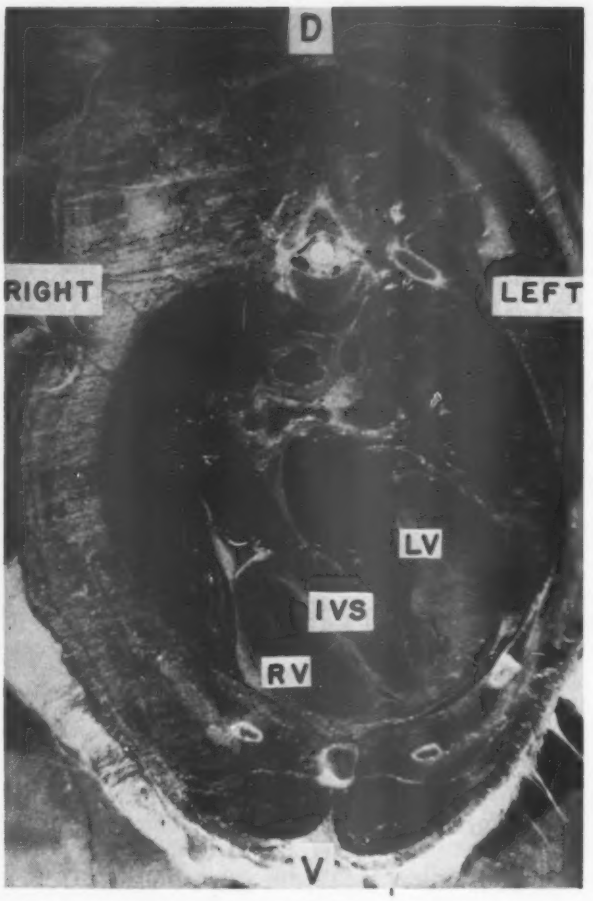


FIG. 6. Cephalic view of horizontal (coronal) cross section of a normal dog at the level of the dorsal spinous process of the seventh thoracic vertebra. Abbreviations as in Figures 4 and 5.

width ratio of 4.5 : 1, and *always* inscribed in a counterclockwise rotation. The projection on the frontal plane forms a long narrow area having an average length-width ratio of 6 : 1. The direction of inscription is more variable in the frontal plane, changing from clockwise to counterclockwise or vice versa with slight rotation of the plane of the loop on its longitudinal axis. In general the direction of inscription in the frontal plane was clockwise.

Major Vectors: Five major vectors of the spatial QRSsÊ loops have been studied and have been designated as vectors 1, 2, 3, 1a and 2a (OA, OC, OE, OF and OH of Fig. 8, respectively). Forces occurring after vector 3 have not been analyzed. Vectors 1, 2 and 3, because of their maximal cephalic-caudal orientation, are readily identified in the frontal and sagittal vectorcardiograms of all dogs. Vectors 1a and 2a, the former having maximal ventral projection and occurring in time between vectors 1 and 2, and the latter having maximal dorsal projection and occurring between vectors 2 and 3, were determined from the projection of the spatial QRSsÊ loop on the horizontal plane. In one dog vector 2a was absent. The five vectors are characterized in Table 1. Figure 9 presents the scatter of the magnitude and direction of these five major vectors.

SPATIAL MAGNITUDE ELECTROCARDIOGRAM (sM ECG)

The sM ECG of the QRS complex forms four basic patterns (Fig. 10). In 50 per cent of cases the sM ECG has three peaks, corresponding in time to the previously designated component parts of the QRSsE loop (Fig. 10A). Peak 2 (caudal portion) always has the greatest height;

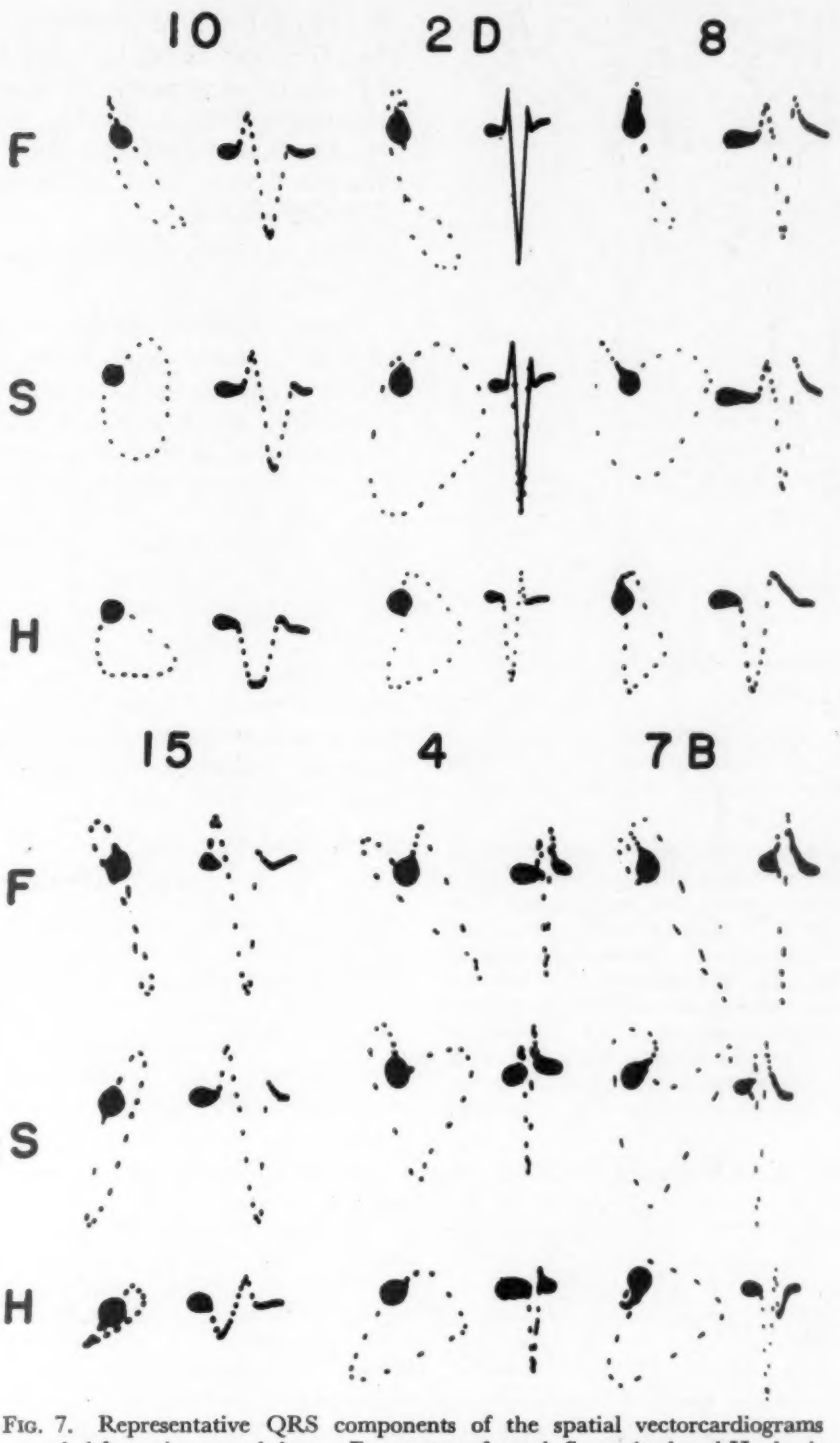


FIG. 7. Representative QRS components of the spatial vectorcardiograms recorded from six normal dogs. F represents frontal, S—sagittal and H—horizontal plane projections. The beam is interrupted 600 times per second. The QRS complex of the scalar electrocardiogram, recorded simultaneously, appears to the right of its respective QRSsÊ loop. This represents the Y component. Limb and thoracic lead electrocardiograms for the same six dogs are shown in Figure 13.

peak 3 (terminal cephalic), the smallest; and peak 1 (initial cephalic) is intermediate. Three distinct variations of this curve occur, dependent upon the spatial magnitude and orientation of certain determining forces to be described as follows.

The sM ECG of the QRS complex consists of peaks 1 and 2 in 20 per cent, peaks 2 and 3 in

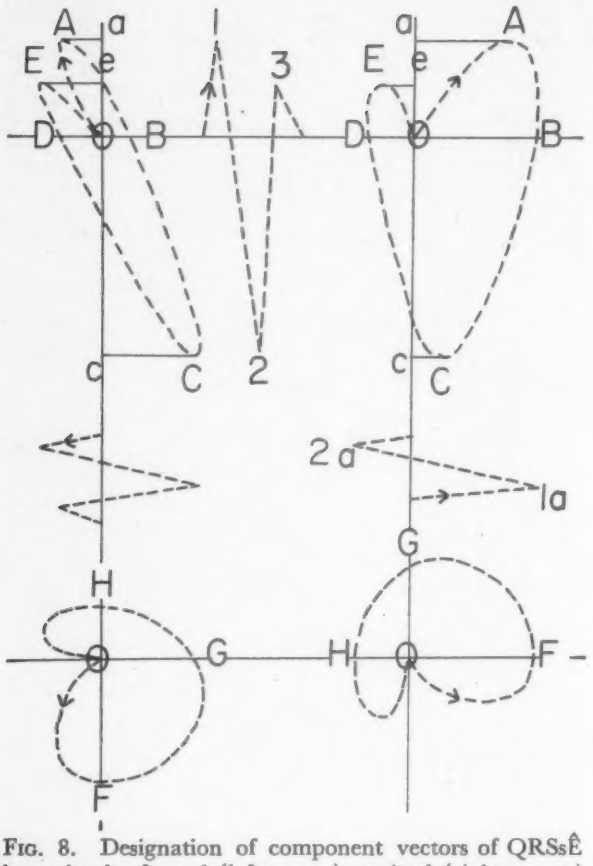


FIG. 8. Designation of component vectors of QRSsÊ loops in the frontal (left upper), sagittal (right upper) and horizontal (lower row) plane projections. The scalar electrocardiogram between frontal and sagittal vectorcardiograms represents Y forces, i.e., inverted left foot lead. The scalar electrocardiogram between frontal and horizontal vectorcardiograms H (left column) represents forces along the X axis, i.e., lead I. The scalar electrocardiogram between sagittal and horizontal vectorcardiograms (right column) represents forces along the Z axis, i.e., back point unipolar lead. (See text.)

20 per cent and of peak 2 in 10 per cent of cases (Fig. 10). Peak 1 or peak 3 is absent when the spatial magnitude of the vector of the cephalic nadir (OA, OE Fig. 10) is less than or equal to that of the vector occurring as the loop changes from caudal to cephalic orientation (OB, OD Fig. 10).

SPATIAL VELOCITY ELECTROCARDIOGRAM (sV ECG)

The sV ECG of the QRS complex forms in all cases a curve with three peaks (Fig. 11). The first peak in spatial velocity occurs during inscription of the proximal portion of the initial cephalic, ventral and dextral forces (OA Fig. 8). The second peak is usually higher than the first and occurs during inscription of forces directed caudad, ventrad and sinistrad (BC Fig. 8). The third and maximal peak occurs during inscription of the last half of the caudal, dorsal and slightly dextral forces (CE Fig. 8). The decrease in the velocity between peaks 1 and 2, and peaks 2 and 3 correspond, respectively, to the initial cephalic and the caudal nadirs (Points A and C in Figs. 10 and 11).

ELECTROCARDIOGRAM

A regular sinus rhythm is present with neither atrial nor ventricular premature beats. The durations of the various components of the electrocardiogram are comparable to those reported by others[9,10] and are as follows: P wave, 50.1 milliseconds (SD 8 milliseconds); P-Q interval, 101 milliseconds (SD 18 milliseconds); QRS duration, 54 milliseconds (SD

TABLE 1
Features of the Five Major Vectors of the QRSsÊ Loop in the Frontal, Sagittal and Horizontal Plane Projections of the Normal Dog

Vector	Time After Onset of QRS (milliseconds)	Direction	Angle			Duration of Related Forces* (milliseconds)	ECG Correspondence
			Frontal Plane (degrees)	Sagittal Plane (degrees)	Horizontal Plane (degrees)		
1	6.0 (SD 2.0)	Cephalad ventrad slightly to right	−100.9 (SD 20.8)	−43.7 (SD 15.4)		Cephalad OAB 10.0 (SD 2.7)	Q in aVF
2	21.5 (SD 3.7)	Caudad	73.4 (SD 16.5)	88.8 (SD 16.1)		Caudad BCD 17.5 (SD 0.4)	R in aVF
3	31.7 (SD 5.0)	Dorsad cephalad slightly to right	−92.8 (SD 21.4)	−108.9 (SD 17.0)		Cephalad DEO 6.5 (SD 2.7)	S in aVF
1a	11.7 (SD 3.4)	Ventrad slightly to left			38.2 (SD 22.8)	Ventrad OPG 20.7 (SD 3.7)	R in V_1
2a	27.9 (SD 4.4)	Dorsad slightly to right			−91.3 (SD 29.8)	Dorsad GHO 12.4 (SD 3.5)	S in V_1 and R in V_B

* Arc designations same as those of Figure 8. SD = standard deviation.

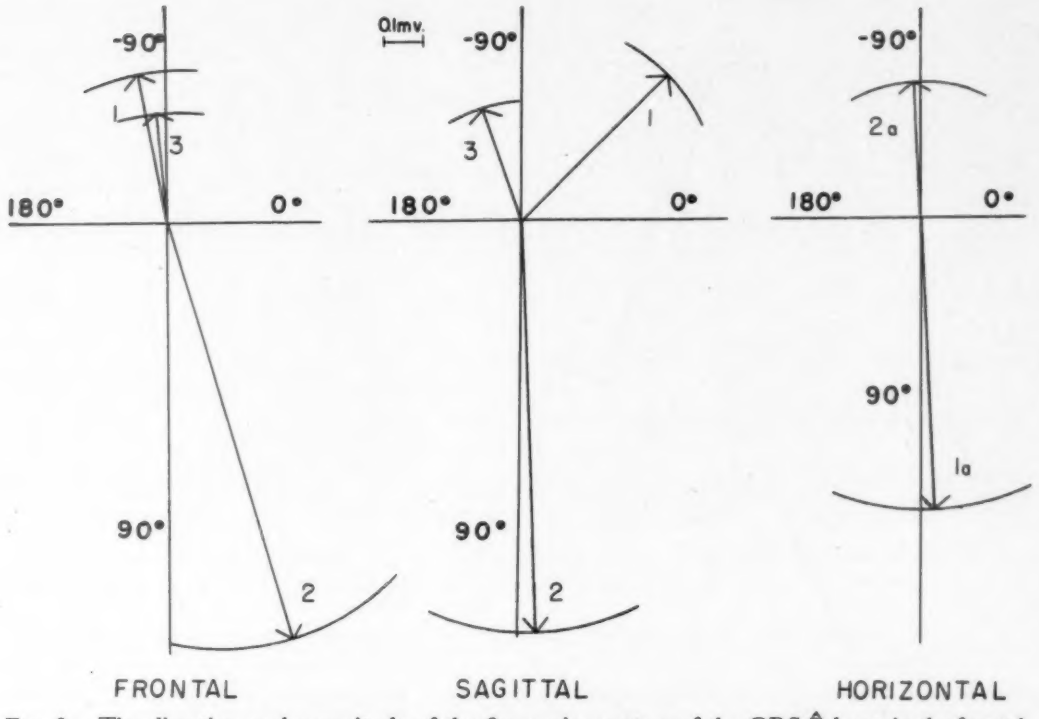


FIG. 9. The direction and magnitude of the five major vectors of the QRSsÊ loops in the frontal, sagittal and horizontal plane projections of the normal dog. The arc at the end of each vector represents one standard deviation of the mean value of the location of the respective vector.

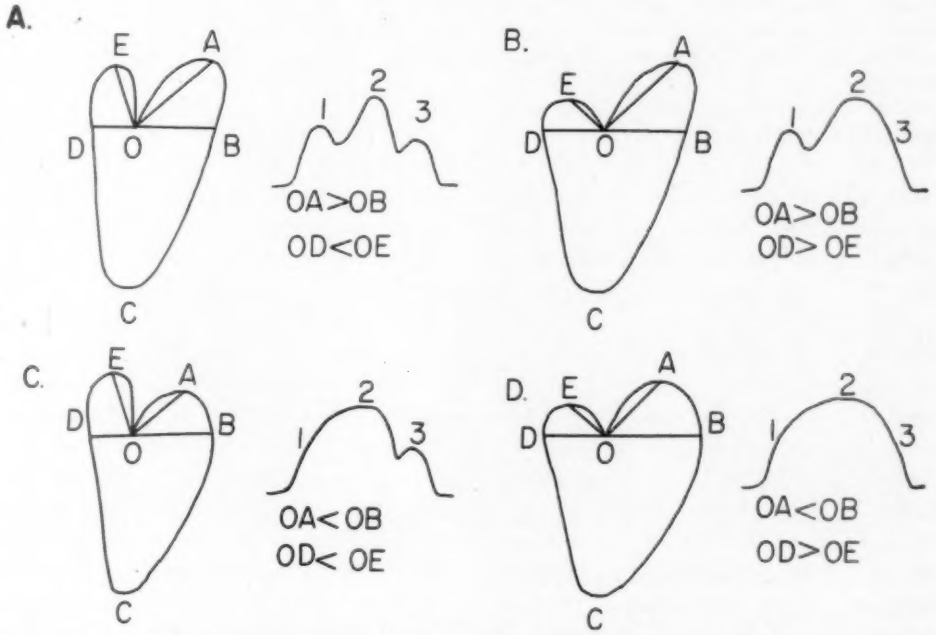


FIG. 10. Variations in contour of the QRS component of the spatial magnitude electrocardiogram. The four basic patterns are determined by the relative magnitude of component pairs of spatial vectors, OA and OB, OD and OE, whose projections on the sagittal plane are shown in this figure. (See text.)

9 milliseconds); Q-T duration, 208 milliseconds (SD 2 milliseconds); R-R interval, 445 milliseconds (SD 79 milliseconds); average heart rate, 134.8 beats per minute (SD 23.8 beats per minute); and K (electrical systole), 313 milliseconds (SD 22 milliseconds). The electrical systole was calculated from Bazett's formula,[11] $K = QT/\sqrt{R-R}$.

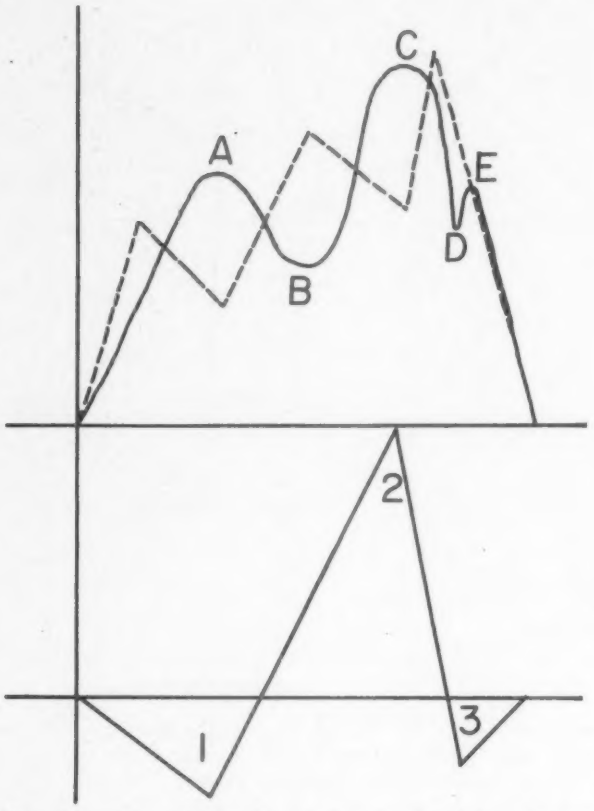


FIG. 11. Interrelationship between spatial velocity electrocardiogram (interrupted line), spatial magnitude electrocardiogram (solid line, upper row) and scalar electrocardiogram (lower row) of the QRS complex. The numbers 1, 2 and 3 indicate the occurrence of vectors 1, 2 and 3. (See text.)

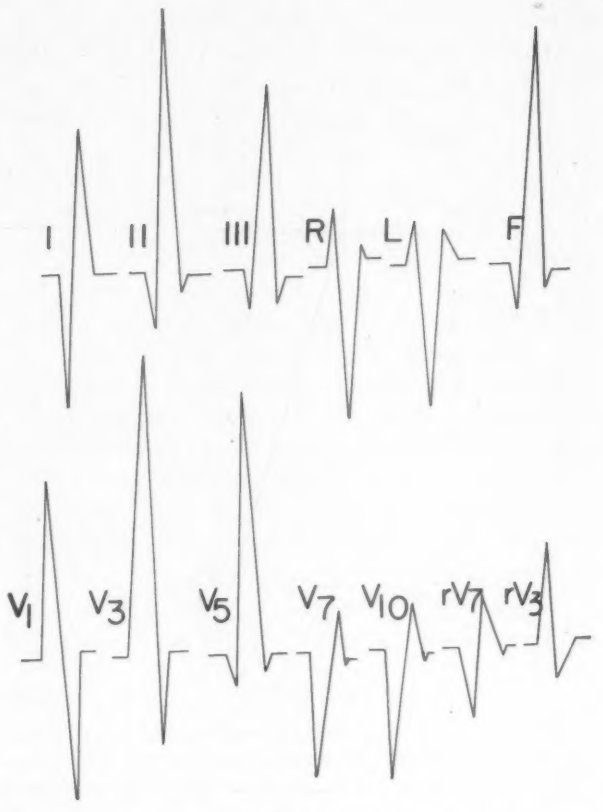


FIG. 12. Characteristic QRS complexes of bipolar and unipolar limb leads, and unipolar circumferential thoracic lead of the normal dog. (See text.)

There is remarkable uniformity in the configuration of the same leads from different animals, including unipolar circumferential thoracic leads and limb leads. Typical QRS complexes are illustrated in Figure 12.

Leads recorded ventrad to the lateral angles of the thorax (rV_3, V_1 and V_3), corresponding to the precordial leads in man, have predominantly Rs deflections, with lead V_1 or V_3 having the largest R waves. The electrode in the V_3 position is located sufficiently dorsad to record a small Q wave in 40 per cent of cases. The electrode in the lead V_5 position is nearly at the "transition" zone, and always records a deep Q wave and an R wave of equal or greater amplitude, and a small S wave. Electrocardiograms recorded from areas dorsad to the angles of the thorax (leads V_7, V_{10} and rV_7) always have Qr or QRs deflections; whereas from the left dorsal quadrant, the r wave is slightly larger than from the right dorsal quadrant. Six representative electrocardiograms are shown in Figure 13.

Comparison of Recorded and Derived Electrocardiograms: The scalar electrocardiograms derived from the QRSsÊ loop in the horizontal plane projection were compared with the actual electrocardiograms (leads rV_7, rV_3, V_1, V_3, V_5 and V_7). In fifteen of twenty-four dogs with technically satisfactory electrocardiograms there was good correlation. Both the actual and derived electrocardiograms show the progression of various electrocardiographic QRS constituents described previously. Consistently the recorded electrocardiograms in leads rV_3, V_1 and V_3 and usually V_5 position show relatively larger R waves than in the derived scalar electrocardiogram (Fig. 14). This difference is possibly due to the proximity of these electrodes to the source of the initial ventral forces.

There are lesser differences between the recorded and derived electrocardiogram in leads V_7, V_{10} and rV_7 positions. The recorded leads from these positions are practically identical to those corresponding leads derived from the QRSsÊ loop in the horizontal plane projection in sixteen cases. In the remainder there are

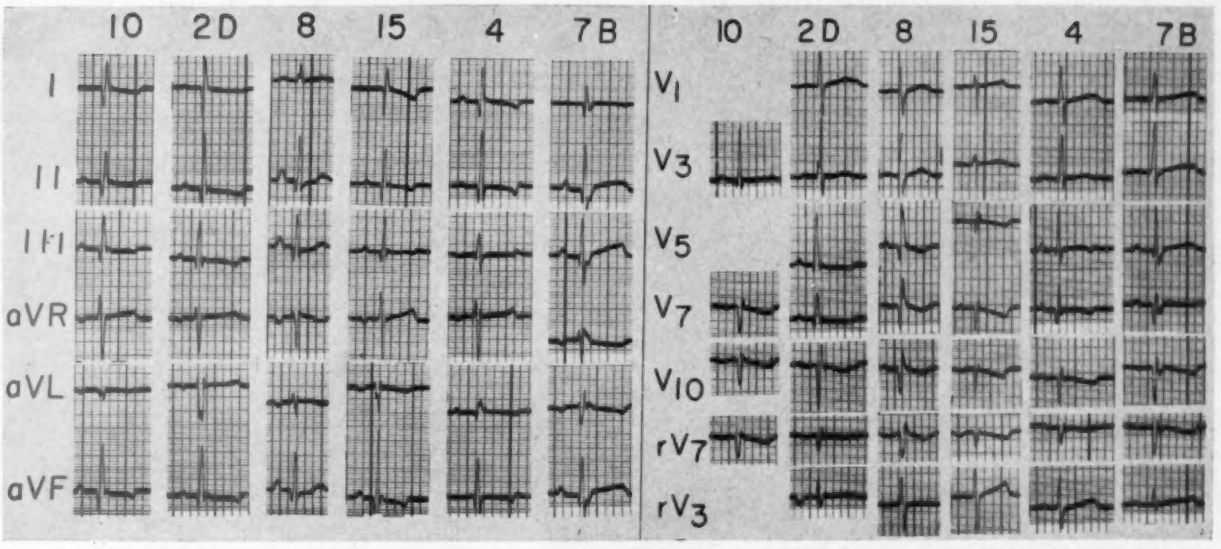


FIG. 13. Representative electrocardiograms of six normal dogs whose vectorcardiograms are shown in Figure 7. The circumferential thoracic leads are designated according to schema of Figure 1. (See text.)

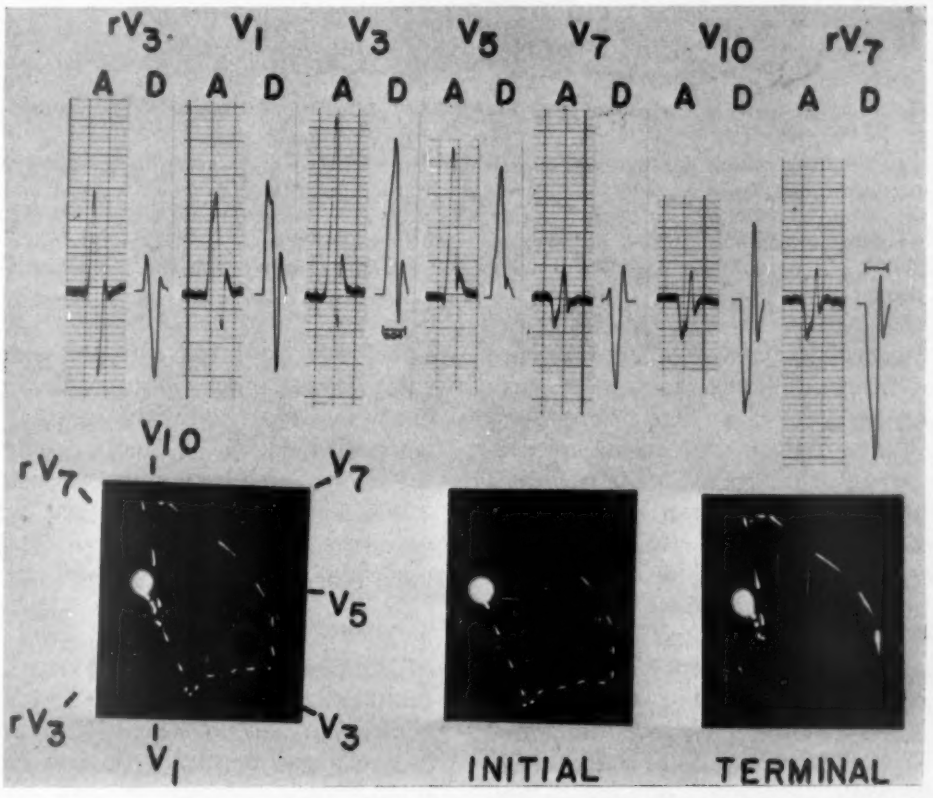


FIG. 14A. Correlation between QRS complexes recorded from unipolar thoracic leads and those derived from the QRSsÊ loops in the horizontal plane projections. (See text.) The correlation is excellent. Note that the R wave is relatively larger in leads rV_3, V_1, V_3 and V_5 of the actual electrocardiogram.

slight differences: in seven cases the recorded electrocardiograms have slightly smaller R waves and larger S waves than in the derived; and in one case the reverse is true.

In five cases leads rV_3, V_1, V_3 and usually V_5 have small Q waves which are absent in the scalar derived electrocardiograms. In addition, the R wave is smaller and the S wave larger than in the derived electrocardiogram.

Thus there are apparent discrepancies be-

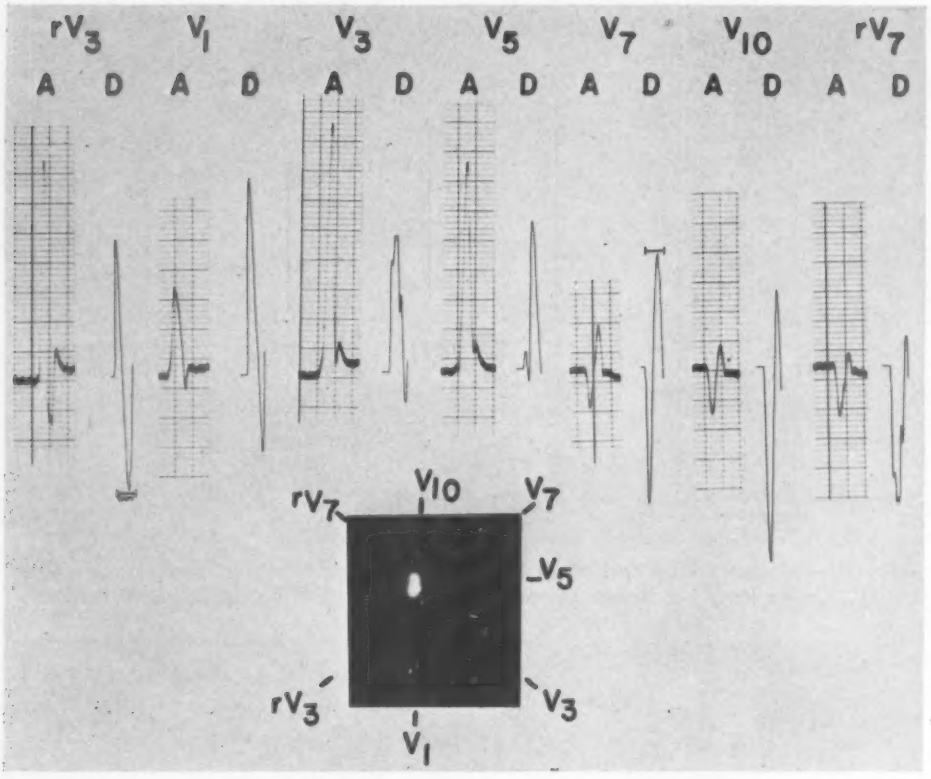


FIG. 14B. Apparent discrepancy between derived lead V_3 which shows an S wave not present in the recorded lead V_3. A scalar electrocardiogram derived from the three-dimensional model from a point 30 degrees caudad from the horizontal (coronal) plane through the origin of the loop was identical with the recorded lead V_3. The difference in lead V_5 (S wave in derived electrocardiogram) was abolished by moving the position of the electrode in the lead V_5 position ventrally approximately 6 degrees.

tween the recorded electrocardiograms and those derived from the QRSsÊ loop in the horizontal plane projection. These are termed "apparent" because, when the spatial orientation of the electrocardiographic electrodes is considered in relation to the *spatial* QRS loop, there is a better correlation. When the exploring "chest" electrode is moved cephalad or caudad to the horizontal plane through the origin of the three-dimensional models, the derived scalar electrocardiograms compare more favorably with the recorded electrocardiograms (Fig. 14). In the five cases mentioned previously in which the recorded electrocardiograms show small Q waves, smaller R and larger S waves than in the electrocardiogram derived from the QRSsÊ loop in the horizontal projection, movement of the exploring electrode 15 to 20 degrees caudad from the horizontal plane through the origin of the spatial model yields derived electrocardiograms with the aforementioned features.

It is our impression that the derived scalar and actual surface electrocardiograms were sufficiently similar in configuration to provide comparable clinical information in the normal dog. However, as in the case of human electrocardiography, it remains to be shown that the same interpretations can be made in diseased states from the vector-derived scalar electrocardiograms as made independently from unipolar exploring surface leads.

ANATOMIC STUDY

The free wall of the right ventricle is located cephalad, ventrad and dextrad to the interventricular septum (Figs. 4, 5 and 6). The free wall of the left ventricle (which is approximately 2.6 times thicker than the right) is located caudad, dorsad and sinistrad to both the interventricular septum and the free wall of the right ventricle. The inflow tract of the left ventricle (diaphragmatic or caudal portion) forms an angle of approximately 60° with the longitudinal axis of the body. The plane of the interventricular septum lies on the plus 30°–minus 150° axis of the sagittal plane cross section, on the plus 140°–minus 40° axis of the fron-

tal plane cross section, and on the plus 50°–minus 130° axis of the coronal plane cross section. Thus, the left side of the interventricular septum faces sinistrad, caudad and dorsad.

Comments

In the present study there is a remarkable consistency and interrelationship between the spatial vectorcardiogram, scalar electrocardiograms, spatial magnitude electrocardiograms and spatial velocity electrocardiograms. Similar configurations and direction of inscription of the vectorcardiogram of the normal dog have been reported by Horan, Burch and Cronvich.[1] In the subsequent discussion we have assumed, as have others, that this electrical activity, as measured by electrodes placed on the body surface, represents the summation of activation potentials of the various areas in the ventricles.[12–16] The *measured* electrical activity is recognized to be the resultant of the cancellation and summation of simultaneously occurring forces. In an earlier report we have noted the uncancelling effect of forces in experimental coronary occlusion.[17]

Relationship of Activation and Anatomic Location of the Ventricles to the Major Vectors of the QRS Component of the Vectorcardiogram: Our study is compatible with the concept that the ventricular activation process may be divided into three major vectors, the order and magnitude of which may be related to the anatomic location and activation of specific parts of the ventricles.[2,12–16] The following correlation between the location of specific anatomic structures and their vectoral electrical equivalent is offered as a first approximation although it would not be altered significantly by shifts of 20 to 30 degrees on any axis.

According to our anatomic studies, an imaginary arrow perpendicular to the plane of the interventricular septum would be located approximately on the minus 130° axis in the frontal plane projection and on the minus 60° axis in the sagittal plane projection. This corresponds well to the location of vector 1 which is on the minus 100.9° axis in the frontal plane projection, and on the minus 43.7° axis in the sagittal plane projection. Vector 1, produced by the early left-to-right activation of the interventricular septum,[12–15] represents the electrical as well as the anatomic dominance of left-to-right forces over right-to-left forces.[15] During this activation, the spatial magnitude electrocardiogram reaches its first peak; the spatial velocity electrocardiogram reaches its first peak followed by a drop; and the electrocardiogram shows a Q wave in leads aVF and I, and an R wave in lead V_1.

The second major vector of the ventricular activation process occurs about 22 milliseconds after the onset of the QRS complex. There is general agreement that during this period multiple regions of the ventricular mass are being activated: the greatest part of the apex, the major part of the free wall of the left ventricle and a smaller area of the anterior wall of the right ventricle.[13,15] The location of vector 2 of the QRSsÊ loop, plus 73.4° in the frontal plane projection and plus 88.8° in the sagittal plane projection, is remarkably similar to the anatomic location of the apex and adjacent free wall of the left ventricle (Figs. 4–6). During the inscription of vector 2, the spatial magnitude electrocardiogram reaches its second and maximal peak; the spatial velocity electrocardiogram divides the period successively into a rapid, reduced and a most rapid phase; and the electrocardiogram shows an R wave in leads aVF, I and V_1 (Fig. 11).

During the period of inscription of the third vector 32 milliseconds after the onset of the QRS, there is activation of basilar portions of both the left and right ventricles and the interventricular septum.[13,14] According to our anatomic studies, these areas are located cephalad, dorsad and slightly dextrad, similar to the location of vector 3. During vector 3 the spatial magnitude electrocardiogram attains its third and minimal peak; the spatial velocity electrocardiogram decreases; and the electrocardiogram shows an S wave in leads aVF and V_1, and an isoelectric termination in lead I.

The Spatial Magnitude Electrocardiogram (sM ECG): The sM ECG is a relatively new method for studying cardiac electrical activity.[4] It represents the total resultant spatial magnitude of the equivalent cardiac vector as a function of time.[4] The wave forms described for man,[4,18,19] the rabbit,[20] and the rat[19] are similar to those of the normal dog obtained in the present study. As mentioned before, peaks 1, 2 and 3 of the sM ECG of the QRS complex (A, C, E of Fig. 11) correspond to vectors 1, 2, 3, respectively, of the QRSsÊ loop. The amplitude of the three peaks appears to be related to the order and amount of myocardium activated. This is suggested by the fact that

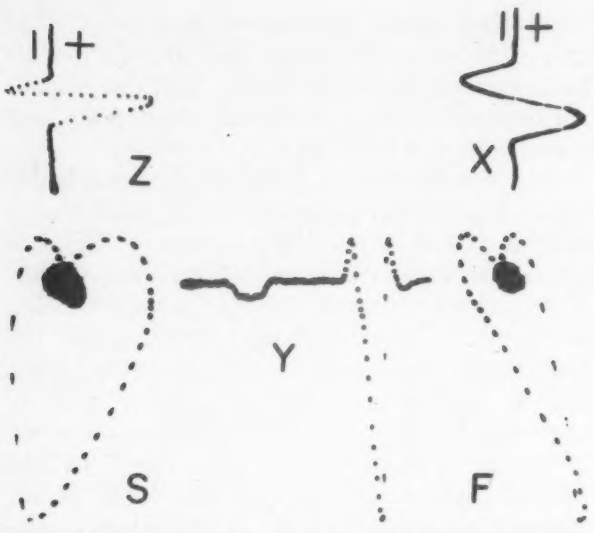


FIG. 15A. The frontal (F) and sagittal (S) plane projections of the QRSsÊ loop of a normal dog. X, Y and Z represent the scalar electrocardiograms comprising the sVCG.

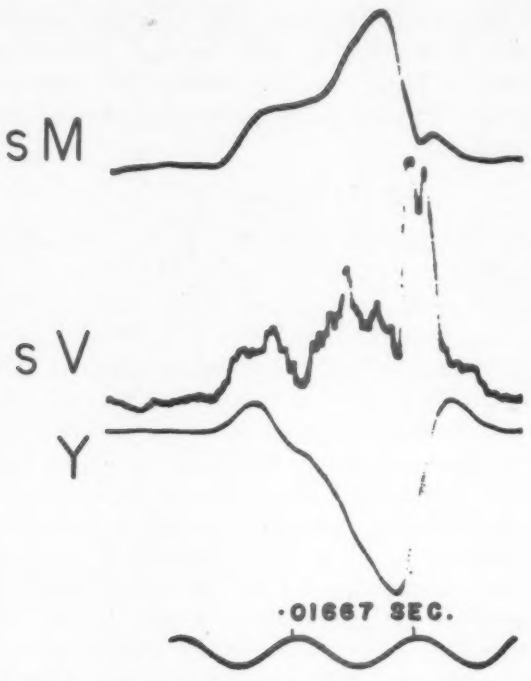


FIG. 15B. The simultaneously recorded spatial magnitude (sM) and spatial velocity (sV) electrocardiograms of the QRS complex obtained with an analog computer are similar to those obtained by calculation and reported in the present study. Y represents the vertical component in the frontal plane, i.e., inverted left foot lead.

the height of peak 2 is greater than that of peak 1 which is greater than that of peak 3; also, the mass of the left ventricle whose predominant activation corresponds to peak 2 exceeds that of the interventricular septum whose activation corresponds to peak 1; this in turn is greater than that of the basilar portion of the ventricles whose activation corresponds to peak 3.

In the previous discussion it has been implicit and stated that the electrocardiogram obtained is not directly proportional to the total electrical activity of the heart, but only to the residual unbalanced currents of the heart within the body.[4] Disturbance in the order of activation or change in the mass of muscle to be activated would be expected to change the degree of cancellation, and hence the form of the spatial magnitude electrocardiogram. This effect has been observed in our recent studies of the effect of experimental coronary occlusion on the spatial magnitude electrocardiogram.[17]

Spatial Velocity Electrocardiogram (sV ECG): The sV ECG is an entirely new and as far as we know previously unpublished method for studying the heart's electrical activity. The sV ECG may be approximated by inspection of the distance between the time interruptions in the spatial loop either by our method of calculation or by an analog computer. Since this study was completed, we have constructed an analog computer which performs the necessary functions electronically to obtain spatial magnitude and velocity electrocardiograms (Fig. 15). The spatial velocity electrocardiogram of the QRS complex does not represent the velocity with which the activation process traverses the myocardium, but instead registers changes in spatial angles and in spatial magnitudes between consecutive vectors.

The component portions of the spatial velocity electrocardiogram of the QRS complex can be related to the ventricular activation process. Peaks 1, 2 and 3 occur approximately 4 to 6 milliseconds before vectors 1, 2 and 3 of the QRSsÊ loop, respectively. Peak 1 represents the initial increase in magnitude from the resting state of the termini of successive vector forces originating in the leftward septal activation. Peak 2 represents a rapid angular displacement of the termini of forces produced by the predominant activation of greater left ventricular forces located about 120° away from those forces producing vector 1. Peak 3 is the largest and represents the movement of the termini of successive spatial vectors from vector 2 to vector 3, roughly through an arc of 180°. The "valleys" between peaks 1 and 2, and 2 and 3 represent the continued and localized activation, respectively, of areas of the inter-

ventricular septum, and the apex and free wall of the left ventricle.

Summary

The ventricular activation process (QRS) of forty healthy dogs was studied by means of vectorcardiograms using Wilson's equilateral-tetrahedral reference system, scalar electrocardiograms, and by constructing spatial magnitude electrocardiograms and spatial velocity electrocardiograms. These data were correlated with anatomic cross sections through corresponding planes of the frozen animal. An attempt was made to correlate the electrical activity, as measured by electrodes placed on the body surface, with the ventricular activation process.

The typical QRSsÊ loop was roughly heart-shaped, and was almost coplanar with the median sagittal plane. Good correlation existed between the actual circumferential thoracic leads and the derived scalar electrocardiograms. Apparent variations between the actual electrocardiogram and those derived from the QRSsÊ loops in the horizontal plane projection were explained on the basis of spatial orientation of the exploring electrode.

The electrical activity of the dog's heart has been presented in three divisions based on time and the areas of the ventricles activated. Activation of the interventricular septum from left-to-right constitutes the 6 milliseconds vector which is directed cephalad, ventrad and slightly dextrad. The spatial magnitude electrocardiogram of the QRS complex reaches its first peak during this period, while the spatial velocity electrocardiogram of the QRS complex reaches its first peak and following dip. Simultaneous activation of the apex and free wall of the left ventricle constitutes the 22 milliseconds vector which is directed caudad with little ventral and sinistral orientation. The spatial magnitude electrocardiogram reaches its second and maximal peak during this period, while the spatial velocity electrocardiogram reaches its second peak, a brief dip and its third and maximal peak.

Activation of the basilar areas of both ventricles and the interventricular septum constitutes the 32 milliseconds vector which is directed cephalad and dorsad, with slight dextral orientation. The spatial magnitude electrocardiogram reaches its third and minimal peak during this period, while the spatial velocity electrocardiogram continues to decline.

References

1. Horan, L., Burch, G. E. and Cronvich, J. A. Spatial vectorcardiograms in normal dogs. *Circulation Res.*, 5: 133, 1957.
2. Sodi-Pallares, D., Brancato, R. W., Pileggi, F., Medrano, G. A., Bisterri, A. and Barbato, E. The ventricular activation and the vectorcardiographic curve. *Am. Heart J.*, 54: 498, 1957.
3. Hellerstein, H. K., Shaw, D. and Sano, T. Dissection of the vectorcardiogram: differential vectorcardiography. *Am. Heart J.*, 47: 887, 1954.
4. Sayers, B. McA., Silberberg, F. G. and Durie, D. F. The electrocardiographic spatial magnitude curve in man. *Am. Heart J.*, 49: 323, 1955.
5. Sayers, B. McA. A spatial magnitude electrocardiograph. *Am. Heart J.*, 49: 336, 1955.
6. Abildskov, J. A., Burch, G. E. and Cronvich, J. A. The validity of the equilateral tetrahedron as a spatial reference system. *Circulation*, 2: 122, 1950.
7. Cronvich, J. A., Conway, J. P. and Burch, G. E. Standardizing factors in electrocardiography. *Circulation*, 2: 111, 1950.
8. Helm, R. A. Vectorcardiographic notation. *Circulation*, 13: 581, 1956.
9. Lannek, N. A Clinical and Experimental Study on the Electrocardiogram in Dogs, pp. 1–189, Stockholm, Sweden, 1949. Ivar Haeggstroms.
10. Lepeschkin, E. Modern Electrocardiography, vol. 1, p. 201. Baltimore, 1951. Williams & Wilkins Co.
11. Bazett, H. C. An analysis of the time-relations of electrocardiograms. *Heart*, 7: 353, 1918.
12. Scher, A. M., Young, A. C., Malmgren, A. L. and Erickson, R. V. Activation of the interventricular septum. *Circulation Res.*, 3: 56, 1955.
13. Scher, A. M., Young, A. C., Malmgren, A. L. and Paton, R. R. Spread of electrical activity through the wall of the ventricle. *Circulation Res.*, 1: 539, 1953.
14. Scher, A. M. and Young, A. C. The pathway of ventricular depolarization in the dog. *Circulation Res.*, 4: 461, 1956.
15. Sodi-Pallares, D. and Calder, R. M. New Basis of Electrocardiography, p. 372. St. Louis, 1956. C. V. Mosby.
16. Penaloza, D. and Tranchesi, J. The three main vectors of the ventricular activation process in the normal human heart. I. Its significance. *Am. Heart J.*, 49: 51, 1955.
17. Hellerstein, H. K. and Hamlin, R. Studies in differential vectorcardiography of the dog. II. Early changes in the QRS vectorcardiogram and electrocardiogram following experimental left circumflex coronary artery occlusion. In: Proceedings Twenty-ninth Scientific Session of the American Heart Association, Cincinnati, October 1956.
18. Abildskov, J. A., Hisey, B. L. and Ingerson, E. E. The magnitude and orientation of ventricular excitation vectors in the normal heart and following myocardial infarction. *Am. Heart J.*, 55: 104, 1958.
19. Hellerstein, H. K. Unpublished observations.
20. Sayers, B. and Silberberg, M. B. Further studies of the electrocardiographic spatial magnitude curve (in the rabbit). *Am. Heart J.*, 53: 558, 1957.

New Methods

A New Technic for Left Ventricular Angiocardiography and Transseptal Left Heart Catheterization*

EDWIN C. BROCKENBROUGH, M.D. *and* EUGENE BRAUNWALD, M.D.

Bethesda, Maryland

EXPERIENCES with transseptal left heart catheterization in 300 patients at the National Heart Institute have demonstrated the advantages of this approach in comparison to other methods of left heart catheterization.[1–4] Although a modified transseptal needle has been employed for left atrial angiocardiography,[3] it had previously not been possible to carry out selective left ventricular angiocardiography, a procedure of considerably greater clinical importance. Accordingly, efforts have been directed toward extending the usefulness of transseptal left heart catheterization by modifying the procedure so as to permit selective left atrial or left ventricular angiocardiography. A technic which would permit the transseptal passage of a flexible radiopaque catheter of sufficient caliber to permit angiocardiography would also provide a better frequency response than the small polyethylene catheter previously employed, as well as means for sampling blood from the left ventricle. Finally, the use of a percutaneous technic for introducing such a catheter would obviate the necessity for exposing and ligating the saphenous vein. The present report constitutes a brief description of this new technic and of our initial clinical experiences with it.

METHOD

Percutaneous puncture of the right femoral vein is carried out with a #16 gauge needle. A flexible coiled spring guide wire is then passed into the vein through the needle, in the manner described by Seldinger,[5] following which the needle is removed. A radiopaque polyethylene catheter,† 70 cm. in length, with an internal diameter of 1.15 mm. and an outer diameter of 2.30 mm., and with the curvature of the distal end preset as in Figure 1A, is introduced over the guide wire and advanced well into the femoral vein. The guide wire is then withdrawn. In order to straighten out the loop and to facilitate placing the catheter in the right atrium, a stylet made of 19 gauge hypodermic tubing, 5 mm. shorter than the catheter (Fig. 1B), is inserted into and advanced with the catheter. After the catheter is positioned in the right atrium, the stylet is replaced by a 19 gauge transseptal needle, 71 cm. in length (Fig. 1C).

When the catheter and needle have been correctly positioned against the interatrial septum in the region of the fossa ovale, puncture of the septum is carried out by advancing the needle tip in the manner previously described[3] (Fig. 1E). Entry into the left atrium is confirmed by pressure measurements and the free withdrawal of oxygenated blood. The catheter, its end tapered to facilitate passage across the interatrial septum (Fig. 1D), is then advanced with the needle until both lie within the left atrium (Fig. 1F). With the needle held in place, the catheter is then slipped over the end of the needle and with the aid of the preset curvature of the distal end, is directed into the left ventricle (Fig. 1G). The needle may then be completely withdrawn (Fig. 2) and an adapter attached to the free end of the catheter. Left ventricular pressure is recorded from the catheter. Selective left ventricular angiocardiography may also be carried out, or by withdrawing the catheter the radiopaque dye may be injected into the left atrium. Upon completion of the study the catheter is withdrawn and gentle pressure is applied to the point of

† Odman-Ledin, supplied by Picker X-ray Corp. Cat. No. 17.887-2.

* From the Clinic of Surgery, National Heart Institute, Bethesda, Maryland.

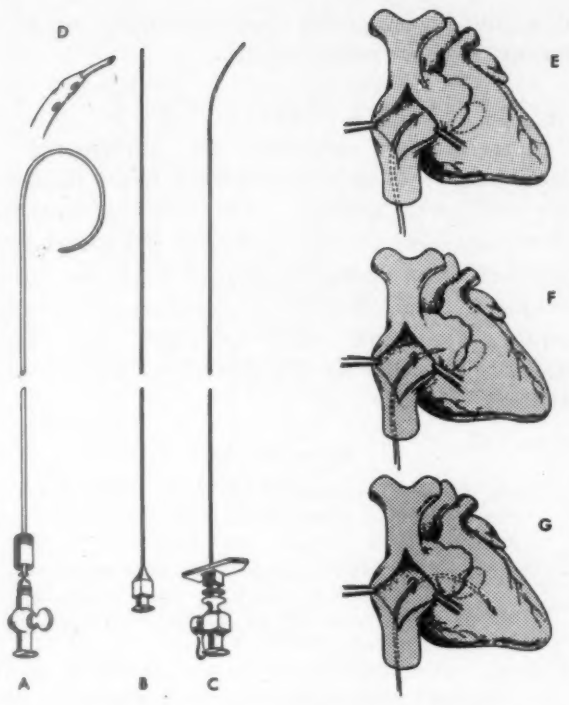


FIG. 1. Drawings of the equipment (A to D) and technic (E to G) employed in the percutaneous method of transseptal left heart catheterization.

entry into the femoral vein in the groin until bleeding ceases.

CLINICAL EXPERIENCES

Left heart catheterization with this technic has been carried out in thirty patients ranging in age from four to forty-seven years. There have been no significant complications. Eight patients have had angiocardiography with either left ventricular or left atrial injections. A representative angiocardiogram is reproduced in Figure 3. It was anticipated that recoil of the catheter into the left atrium during left ventricular injection would present a problem, but so far this has not been serious. The left ventricle was entered in twenty-nine of the patients. Although final comparison must await further experience, it is possible that passage of the catheter into the left ventricle can be performed with greater regularity by this technic than with the polyethylene catheter which cannot be manipulated under fluoroscopic control.

Although the external diameter of the catheter is slightly larger than that of the 17

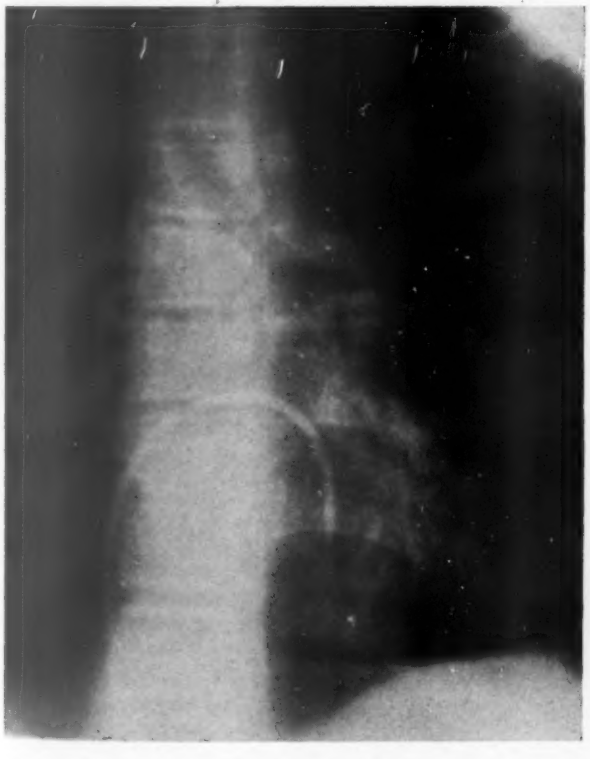


FIG. 2. Roentgenogram showing the catheter traversing in turn the right atrium, interatrial septum, left atrium and mitral valve. The opening of the catheter is in the left ventricular cavity.

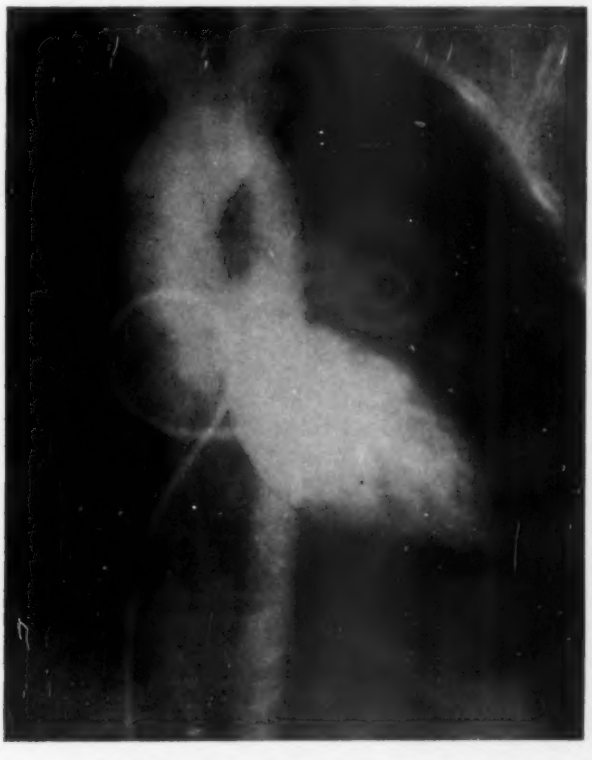


FIG. 3. Left ventricular angiocardiogram performed by the percutaneous transseptal technic in an eight year old boy with congenital valvular aortic stenosis.

gauge transseptal needle, it is believed that, as with the needle, no persistent opening in the septum will result. Krypton[85] inhalation tests[6] have shown no evidence of a left-to-right shunt in three patients following the procedure described herein. Two dogs in which this procedure was performed were sacrificed two weeks later and their atrial septa were found to be intact. No instances of phlebitis have been encountered.

The technic described is designed to permit left heart angiocardiography to be performed in the course of left heart catheterization without the hazards attendant upon percutaneous left ventricular puncture and without the difficulties involved with retrograde left ventricular catheterization. In addition, when only left heart catheterization is employed, the percutaneous approach described permits the procedure to be accomplished without surgically excising and ligating the saphenous vein. Thus, if necessary, multiple catheterizations may be carried out in any given patient.

The catheter employed is of sufficient size to permit the sampling of blood and its larger lumen certainly improves the quality of the left ventricular pressure pulse tracings. Removal of the needle following positioning of the catheter in the left ventricle enables the patient to be exercised with a standard bicycle ergometer. Since it is also possible to perform both right and left heart catheterizations using the same percutaneous puncture, a complete hemodynamic investigation may be carried out in a relatively short period of time.

Summary

A technic is described for introducing a radiopaque catheter into the left heart through the interatrial septum. The chief advantages of the method are that selective left atrial and ventricular angiocardiography may be conveniently performed in conjunction with transseptal left heart catheterization and that surgical exposure of the saphenous vein is not necessary.

References

1. Ross, J., Jr. Transseptal left heart catheterization. A new method of left atrial puncture. *Ann. Surg.*, 149: 395, 1959.
2. Ross, J., Jr., Braunwald, E. and Morrow, A. G. Transseptal left atrial puncture: new technique for the measurement of left atrial pressure in man. *Am. J. Cardiol.*, 3: 653, 1959.
3. Ross, J., Jr., Braunwald, E. and Morrow, A. G. Left heart catheterization by the transseptal route: a description of the technique and its applications. *Circulation*, in press.
4. Cope, C. Technique for transseptal catheterization of the left atrium: preliminary report. *J. Thoracic Surg.*, 37: 482, 1959.
5. Seldinger, S. I. Catheter replacement of the needle in percutaneous arteriography. *Acta radiol.*, 39: 368, 1953.
6. Sanders, R. J. and Morrow, A. G. The identification and quantification of left to right circulatory shunts: a new diagnostic method utilizing the inhalation of a radioactive gas, Kr^{85}. *Am. J. Med.*, 26: 508, 1959.

Thermal Dilution Curves in the Study of Circulatory Shunts

Instrumentation and Clinical Applications*

THEODORE COOPER, M.D., EUGENE BRAUNWALD, M.D., GRANT C. RIGGLE, B.S., E.E. *and* ANDREW G. MORROW, M.D.

Bethesda, Maryland

INDICATOR DILUTION curves constitute one of the most useful technics in the recognition and localization of circulatory shunts.[1,2] The necessity for the withdrawal of significant quantities of blood and the distortion in the dilution curve imposed by the sampling system[3] have prompted the development of technics permitting introduction of the detecting element directly into the blood stream.[4–7] The feasibility of recording intravascular dilution curves, utilizing a thermal sensitive element as the detector and solutions of cold saline as the indicator, has been demonstrated in the experimental animal.[8–11] The present report describes the technic and instrumentation which have been developed to facilitate the application of this approach to the characterization of circulatory shunts in patients with congenital heart disease.

INSTRUMENTATION

The detector, a glass-imbedded thermistor, VECO 32A49, constituted one arm of a battery powered wheatstone bridge. Intra-arterial detection was accomplished with the thermistor incorporated in the tip of a 20 gauge hypodermic needle†, or in a 20 cm. segment of polyethylene or Teflon® tubing introduced through an 18 gauge Cournand needle. Sterilization by means of autoclaving was possible with the hypodermic needle and the Teflon catheter. Intracardiac temperatures were sensed with a thermistor incorporated into the tip of a 150 cm. long Teflon catheter (0.30 in. outer diameter). The latter was advanced through the cardiac catheter so that its tip just protruded into the blood stream. At the time of cardiac surgery thermal dilution curves were obtained from any desired intracardiac site by direct puncture with the 20 gauge needle which housed the thermistor in its tip. Although the time constant of the thermistor is 0.2 second, when mounted into the probe of the catheter or hypodermic needle it was increased to 0.4 to 0.7 second.

The signal produced by temperature alterations was amplified by a transistorized d.c. circuit‡ to a level of 0.2–0.5 volts (Fig. 1), and was led into a millivolt recorder§ or a d.c. amplifier coupled with an oscillographic photographic recorder.‖ The system was found to be linear over a wide range of temperatures (Fig. 2). The instrument was designed to permit absolute measurement of the blood temperature by comparing the signal obtained from the thermistor with that resulting from the introduction of previously calibrated variable electrical resistances into the circuit. In addition, the signal resulting from any induced change in blood temperature could be measured precisely by comparing it to the signal obtained from the introduction of a fixed resistance. The latter was known to be equivalent to that resulting from a change in temperature of the thermistor of 0.1°C. Stability of the amplifier over a wide range of ambient temperatures was accomplished by enclosing the transistor in a 1 inch diameter fiber glass insulation sleeve and allowing the temperature of the transistor to reach ambient level over a period of twenty minutes.

CLINICAL EXPERIENCES

Thermal dilution curves were obtained from

† Yellow Springs Instrument Co., Inc., Yellow, Springs, Ohio.

‡ Modified from a transistorized d.c. amplifier designed by Dr. A. W. Richardson, Dept. of Physiology, St. Louis University.

§ Rectiriter, Texas Instrument Co., Houston, Tex.

‖ DR-8, Electronics for Medicine, White Plains, New York.

* From the Clinic of Surgery, National Heart Institute and the Instrument Development and Engineering Branch, DRS, National Institutes of Health, Bethesda 14, Maryland.

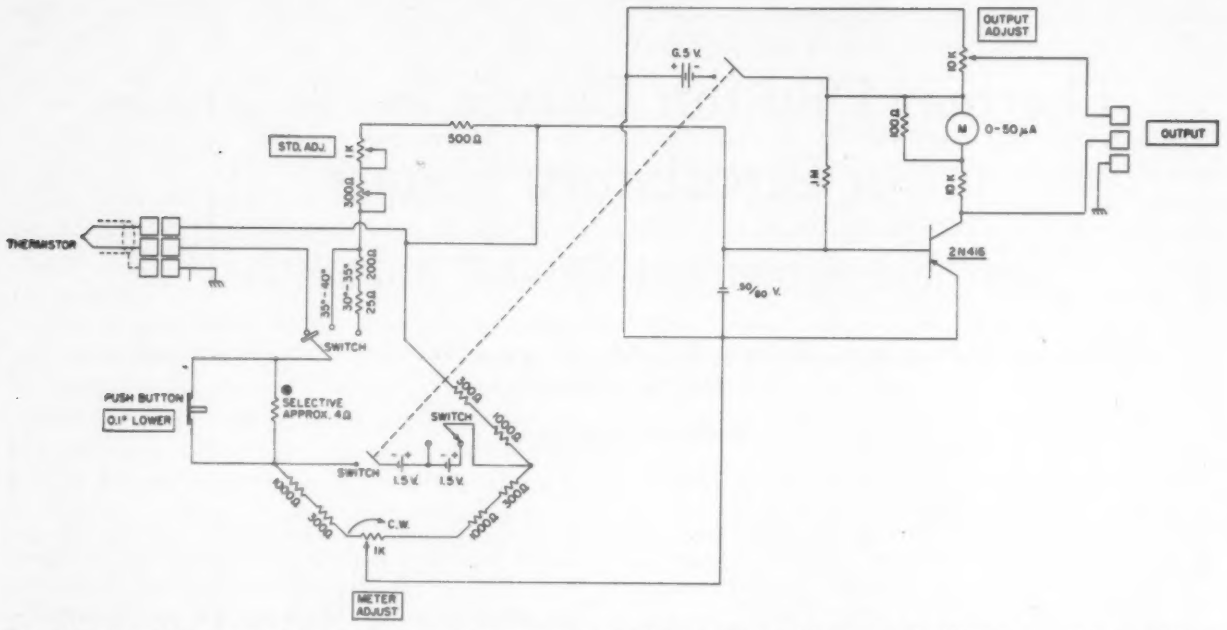


FIG. 1. Circuit diagram of the temperature detector and amplifier. The resistance marked by the asterisk was determined by measurement of the average resistance change resulting from a 0.1 °C. temperature change of the thermistor between 35 ° and 40 °c. and was wound from Nichrome wire.

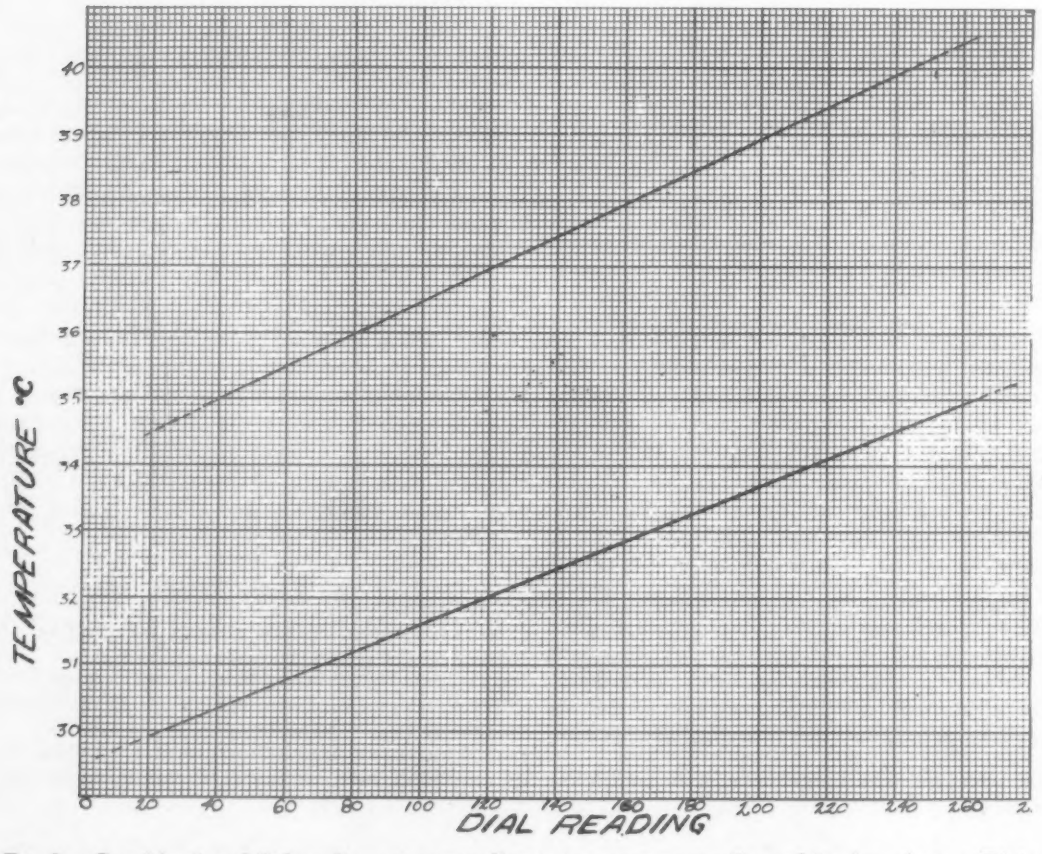


FIG. 2. Graphic plot of dial readings corresponding to temperature readings of the thermistor. Dial reading is directly proportional to resistance change.

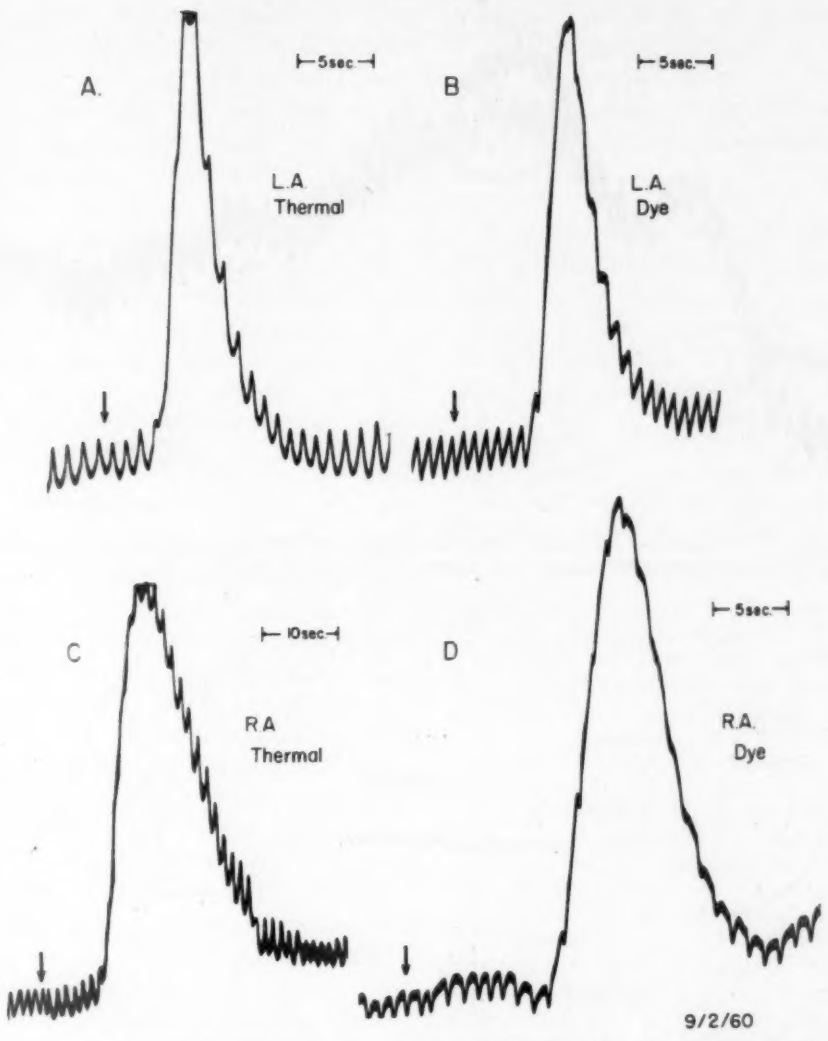


FIG. 3. Thermal (A and C) and dye (B and D) dilution curves from a patient without hemodynamically significant heart disease. The thermal detector was inserted into the brachial artery through a Cournand needle which also served as the sampling site for the dye curves. A, thermal dilution curve obtained following injection of cold saline into left atrium. B, dye curve following injection into left atrium. C, thermal curve following injection into right atrium. D, dye curve following injection into right atrium.

a total of twenty patients during cardiac catheterization or at the time of operation. Dye dilution curves were recorded by means of cardiogreen dye[12] either simultaneously with or immediately after the thermal dilution curves and provided a basis for comparison.

Representative curves are illustrated in Figures 3, 4 and 5. Figure 3 demonstrates arterial thermal and dye dilution curves obtained following left and right atrial injections into an adult patient without hemodynamically significant cardiovascular disease. Following injection of the indicators into the left atrium, the ascending and descending limbs of the two curves are virtually identical. The slightly longer appearance time of the dye curve is due to the delay imposed by the tubing between the arterial needle and the densitometer. Following the injection of cold saline into the right atrium the ascending and descending limbs and appearance time of the thermal curves were slightly prolonged in comparison to the dye dilution curves. None of these curves provided evidence of a circulatory shunt.

Dye and thermal curves recorded simultaneously from the right and left femoral arteries of an eighteen year old girl with a bidirectional shunt through a patent ductus arteriosus are shown in Figure 4. A mixture of cardiogreen dye and cold saline was injected into the out-

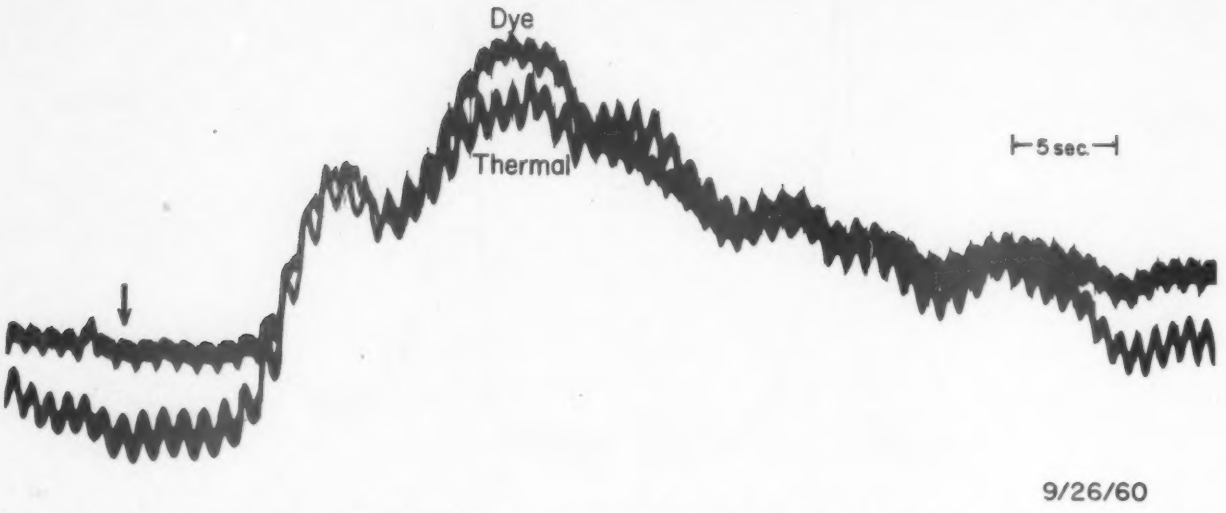


FIG. 4. Simultaneous thermal and dye dilution curves from right and left femoral arteries in a patient with a bidirectional shunt through a patent ductus arteriosus. A mixture of cardiogreen dye and cold saline was injected into the right ventricle.

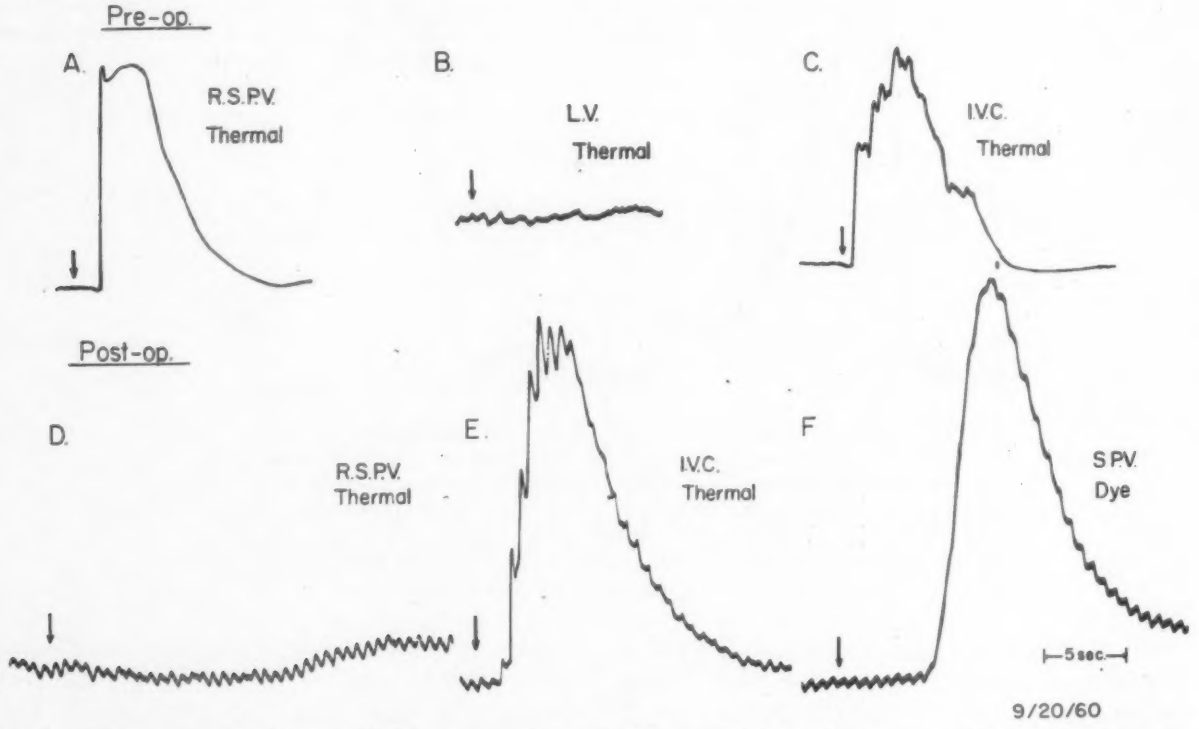


FIG. 5. Pulmonary arterial thermal dilution curves (A to E) and an arterial dye dilution curve (F) obtained from a patient with an uncomplicated ostium secundum atrial septal defect at operation. A, B, C, before the heart was opened. D, E, F, after repair was completed. A, curve following right superior pulmonary vein injection. B, curve following left ventricular injection. C, curve following injection into the inferior vena cava. D, curve following injection into right superior pulmonary vein after repair of defect. E, curve following injection into inferior vena cava after repair. F, radial arterial dye dilution curve obtained following the injection of dye into the right superior pulmonary vein after surgical repair of the defect.

flow tract of the right ventricle. The contours of both curves are essentially identical and reveal an early component signifying a right-to-left shunt, and a prolonged descending limb indicating a left-to-right shunt.

At the time of operation the injection of cold saline into a pulmonary vein of an adult patient with an uncomplicated ostium secundum atrial septal defect was followed by the rapid appearance of the indicator in the pulmonary

artery blood (Fig. 5A). Following injection into the left ventricle no indicator could be detected in the pulmonary artery (Fig. 5B). Injection into the inferior vena cava was followed by a curve in the pulmonary artery which evidenced recirculation[12] (Fig. 5C). After surgical closure of the defect, injection into the pulmonary vein did not result in the appearance of indicator in the pulmonary artery (Fig. 5D), and the injection into the inferior vena cava resulted in a normal dilution curve in the pulmonary artery (Fig. 5E). The absence of a left-to-right shunt was confirmed by the dye dilution curve obtained after pulmonary vein injection and radial artery sampling (Fig. 5F).

Comment

The advantages of the direct intravascular and intracardiac detection of indicator are clear. Numerous curves may be obtained in the course of a single study without the necessity of blood replacement or anticoagulation. This is of greatest importance in the study of infants and children with congenital heart disease. In addition, the problems of skin discoloration and pyrogenic reactions resulting from multiple dye injections are obviated. The hazard of electric shock is prevented by the use of low bridge voltage. The instrumentation is relatively simple, inexpensive and easy to construct. It may be used in conjunction with commercially available thermistor probes and any commercially available millivolt recorder. Sensitivity can be augmented by the use of a d.c. amplifier in series with the transistorized amplifier. This has permitted the use of room temperature saline as the indicator (Fig. 3).

Although slight differences between simultaneously recorded dye and thermal dilution curves have been noted in the dog by Goodyer and associates[10] and were recorded following right heart injections in the patients with no evidence of heart disease (Fig. 3), these differences are of little clinical significance in the characterization of circulatory shunts. The principles of interpretation of the thermal dilution curves for the detection and localization of shunts are identical to those utilized in the analysis of dye dilution curves.[1,2] Since the instrument is linear, it can be calibrated easily and can be used for the quantitative measurement of cardiac output. Adaptation for use at the operating table permits rapid confirmation of the diagnosis before the heart is opened and reliable assessment of the completeness of the repair. The ability to obtain dilution curves without sampling blood is of particular importance in the operating room where the technic and instrumentation required for the inscription of dye dilution curves has proved cumbersome.

Summary

A transistorized d.c. amplifier, which when used with a thermistor permits the recording of stable linear thermal dilution curves, is described. The applicability of the thermal dilution technic to the study of patients with circulatory shunts has been demonstrated.

Acknowledgment

The authors acknowledge the cooperation of Mr. James Gilliam, instrument maker, in the development of the detector probes and catheters.

References

1. Wood, E. H., Swan, H. J. C. and Helmholz, H. F., Jr. Recording and basic patterns of dilution curves. Normal and abnormal. *Proc. Staff. Meet. Mayo Clin.*, 32: 464, 1957.
2. Braunwald, E. and Morrow, A. G. Newer diagnostic technics in congenital heart disease. *Advances Int. Med.*, 10: 41, 1960.
3. Milnor, W. R. and Jose, A. D. Distortion of indictor-dilution curves by sampling systems. *J. Appl. Physiol.*, 15: 177, 1960.
4. Paul, M. H., Rudolph, A. M. and Rappaport, M. D. Temperature dilution curves for the detection of cardiac shunts. *Circulation*, 18: 765, 1958.
5. Clark, L. C., Jr. Intravascular polarographic and potentiometric electrodes for the study of the circulation. *Tr. Am. S. Art. Int. Org.*, 6: 348, 1960.
6. Frommer, P. L., Pfaff, W. W., Braunwald, E. and Morrow, A. G. Application of an intravascular electrode for the recording of indicator dilution curves. *Circulation*, in press.
7. Bender, F. and Seifert, H. H. Zur diagnostischen Arwendung eines Photozellenkatheters. *Ztschr. Kreislaufforsch.*, 47: 260, 1958.
8. Fegler, G. Measurement of cardiac output in anesthetized animals by a thermo-dilution method. *Quart. J. Exper. Physiol.*, 39: 153, 1954.
9. Fegler, G. The reliability of the thermodilution method for determination of the cardiac output and the blood flow in central veins. *Quart. J. Exper. Physiol.*, 42: 254, 1957.
10. Goodyer, A. V. N., Huvos, A., Eckhardt, W. F. and Ostberg, R. Thermal dilution curves in the intact animal. *Circulation Res.*, 7: 432, 1959.
11. Fronek, A. and Ganz, V. Measurement of flow in single blood vessels including cardiac output by local thermodilution. *Circulation Res.*, 8: 175, 1960.
12. Braunwald, E., Pfaff, W. W., Long, R. T. L. and Morrow, A. G. A simplified indicator dilution technic for the localization of left-to-right circulatory shunts. Experimental and clinical study of intravenous injection with right heart sampling. *Circulation*, 20: 875, 1959.

A New Method of Protection Against the Effects of Acceleration on the Cardiovascular System*

MARTIN G. WEBB, JR., LCDR, MC, USN† *and* R. FLANAGAN GRAY
Pensacola, Florida

MAN has suddenly found himself poised on the threshold of space and is confidently preparing for the most dramatic and exciting adventure in his history. This dawning era of space flight may be compared with the "Model T" era of the automobile. Although the present vehicles and equipment may lack the sophistication which will come with future developments and discoveries, they are adequate for the present Man-in-Space program. However, for some of the situations in which man may find himself in the future, whether intentionally or accidentally, most of our present equipment will be inadequate. One such area of inadequacy is that of maintaining man's physiologic integrity during periods of high acceleration stress. The most important physiologic disruptions which occur during acceleration exceeding four to five seconds' duration are those in the cardiovascular system.

EFFECTS OF ACCELERATION ON THE CARDIOVASCULAR SYSTEM

Acceleration is a change in velocity with respect to time. One familiar example is the acceleration produced by gravity on a free-falling object. The free-falling object in a vacuum at the earth's surface will accelerate at the rate of 32 feet/sec./sec. This rate of acceleration is called 1 G (for gravity). A change in velocity of 64 feet/sec./sec. is called 2 G, etc. The force of gravity is defined as the product of mass times the acceleration and manifests itself by weight. The man who weighs 200 pounds at 1 G will weigh 400 pounds at 2 G. Weight variations due to acceleration naturally result in pressure changes and these are most important in fluid systems. For instance, the pressure at the bottom of a column of water 5 feet in height is 2.3 pounds per square inch at 1 G, and twice that amount or 4.6 pounds per square inch at 2 G. Since the cardiovascular system is essentially a hydraulic system, it is evident that acceleration will cause pressure changes in this physiologic fluid system.

Aircraft are so constructed and flight maneuvers are so designed that most of the accelerations experienced during flight are positive accelerations, with the organs being displaced toward the feet. During exposure to acceleration, as in a sharp turn or a pullout from a dive, an aircraft occupant is forced down into his seat. Since the body as a whole is well supported, it does not move relative to the aircraft. However, the blood within the vascular system, being a fluid, is displaced toward the dependent portion of the body due to its increased weight and the resultant increased pressures within the vascular system. As the elastic vessels distend and blood accumulates in the dependent portion of the body, cardiac return is decreased. This accumulation of blood is believed to occur in the splanchnic region and in the superficial vessels of the lower extremities. Due to the increased weight of the blood, it is increasingly difficult for the heart to maintain circulation to the eyes and brain. The result of this decreased cardiac return and increased opposition to cephalad flow is the cessation of circulation through the eyes[1] and brain, which is followed within three to five seconds by blackout and unconsciousness. During high or prolonged acceleration expo-

* From the U. S. Naval Air Development Center, Johnsville, Pennsylvania. The opinions and conclusions contained in this report are those of the authors. They are not to be construed as necessarily reflecting the views or the endorsement of the Navy Department.

† Dr. Webb is now aboard the USS Lake Champlain (CVS-39), Care of Fleet Post Office, New York, New York.

sures, the relatively unsupported capillaries in the skin rupture in the dependent portions of the body and petechiae result. At times these are so numerous as to coalesce almost completely. A marked distention of the superficial veins of the extremities, causing severe pain, is at times the limiting factor in tolerance to moderately high and prolonged accelerations.[2,3] Finally, acceleration may cause cardiac arrhythmias. The incidence of arrhythmias increases with advancing age, higher acceleration levels and fatigue. Isolated premature ventricular beats and premature auricular beats are seen often. Auricular fibrillation, such as reported by Zuidema et al.[4], has occurred in one centrifuged subject at Johnsville.

Present Protective Systems

Antiblackout Suits, Muscle Tensing and Valsalva Maneuvers: To combat the effects of acceleration during flight, antiblackout suits, muscle tensing and a modification of the Valsalva maneuver are used. Antiblackout suits are tight-fitting garments worn over the lower half of the body. Incorporated into each suit are bladders located over the calves, thighs and abdomen. These bladders are interconnected and are attached to a high pressure air source in the aircraft. When the aircraft is subjected to positive acceleration, a piston-type valve in the air line opens. When the high pressure air fills the bladders, the fabric of the suit applies external pressure to the legs and abdomen. This provides counterpressure to the walls of the blood vessels and aids in preventing pooling and vascular distention. Muscle tensing gives support to the deep vessels, and with the antiblackout suit aids cardiac return. An intermittent Valsalva maneuver increases intrathoracic pressure without appreciably decreasing cardiac return. The increased intrathoracic pressure helps to maintain the circulation to the head by decreasing the cephalothoracic pressure difference.

The average tolerance to positive acceleration stress in relaxed, unprotected individuals, using blackout within ten seconds as the end point, is 4 to $4^1/_2$ G. Use of the antiblackout suit, muscle tensing and the intermittent Valsalva maneuver increases this tolerance to about 7 to $7^1/_2$ G. This level of protection is sufficient to protect crew members of present military aircraft against the dramatic effects of acceleration on the cardiovascular system.

Transverse Acceleration: A second method of protection is simply to orient the long axis of the body perpendicular to the acceleration thrust. This is commonly referred to as transverse acceleration and can be in the supine or prone position. In such an orientation the maximum intravascular pressures developed are much less than in the positive G position, since the anteroposterior dimension of the body is but a small fraction of the sitting height. The idea is not new. In 1937 Bührlen[5] was able to attain a level of 17 G in the supine position. In 1958 workers at the Naval Air Development Center[6] found that acceleration as high as 25 G could be tolerated in the supine position. However, the indications are that even at 15 G in the supine position, the centrifuge subjects have experienced difficulty in breathing due to the increased weight of the anterior chest and the abdominal contents. In addition, subjects must concentrate on proper straining technics to prevent impending grayout. Such distractions could prevent full concentration of an astronaut on the complex and critical task of rocket vehicle control. Indeed, performance studies during theoretic rocket re-entry acceleration pattern exposures on the Wright Air Development Center human centrifuge by Clarke et al.[7] have shown that the performance of a simple tracking task deteriorates to a marginal level at 15 G.

A supine position protection system will be used by the Project Mercury astronauts. The system is expected to provide adequate protection for all accelerations to be experienced during the Mercury flights, even during emergency situations.

Water Immersion

As future generations of astronauts push back the frontiers of space, it is likely that they will be exposed occasionally to accelerations of such magnitude that present protective systems will be useless. For instance, a vehicle entering the earth's atmosphere perpendicular to the earth's surface at a velocity of 25,000 m.p.h. would be subjected to an acceleration impulse lasting ten seconds, with a peak of about 320 G. Due to small errors of navigation or guidance, crew members may be subjected to acceleration which is beyond present tolerance limits. It seemed advisable to explore the possibility of developing a system which would protect man against very high accelerations. This demanded a radical departure from present protective systems.

An analysis of the effects of acceleration on the cardiovascular system suggested to Gray[8] that complete immersion in water would offer the greatest chance of success in significantly increasing G tolerance. By completely immersing a man in water within a nonexpandable container, the increased fluid pressure developed within the cardiovascular system during acceleration would be approximately balanced by the gradient of pressure developed in the water outside the body. Thus petechiae, vascular distention, pooling and decreased cardiac return would be partially prevented and circulation to the eyes and brain would be aided. In order to prevent the high water pressure from compressing and possibly causing injury to the thoracic cage, Gray proposed that the rigid container be a closed system, with only the respiratory system of the subject being exposed to ambient air pressure. If the space between the experimental subject and the container were completely filled with water, the increased water pressure resulting from acceleration would not compress the chest until the water pressure external to the chest equaled or exceeded ambient air pressure. An analysis of the anatomic relationships of the cardiovascular system within the chest suggested that the orientation of the subject which would be most compatible with high acceleration tolerance was the prone position. In this position the heart would be supported by the anterior chest wall, and there would be less disturbance of the normal anatomic relationships of the heart and large vessels.

In addition to the excellent protection of the cardiovascular system, it was expected that movement of the extremities in such a system would be possible at high accelerations. If we assume an average specific gravity of 1.07 for the extremities, we arrive at the assumption that in distilled water the extremities would weigh as much at 14 G as they do at 1 G in air. Thus the buoyancy of the body by water would enable a man to operate hand and foot controls at very high acceleration levels.

The limiting factor in this method of protection appeared to be that those portions of the cardiovascular system in air-filled spaces, particularly the chest, would not be supported by a gradient of fluid pressure but by a less satisfactory single air pressure. The increased hydrostatic head of blood within the pulmonary vessels might cause hemorrhages in the anterior portion of the lungs. Also, as the greatest proportion of the lung tissue is displaced anteriorly, the resultant stretching and distention of lung tissue in the posterior chest might cause alveolar rupture and air embolism.

Previous attempts to develop water protection systems were not sufficiently successful to merit operational use. During World War II the Germans[9] experimented with a water device and concluded that greater antiblackout protection could be obtained by use of the antiblackout suit combined with straining in a crouched position. Franks[10] developed a water-filled suit for the British during the same period, but it was not adopted due to the superiority of the pneumatic suit in cost, weight and comfort. The protection afforded by the water-filled suit did not exceed that of the pneumatic suit. In both of the water systems the water height was at about heart level.

Bondurant et al.[11] at the Wright Air Development Center in 1958 experimented with complete submersion in an open tank with the subjects using an aqualung to maintain respiration and to provide the air pressure necessary to prevent a decrease in chest volume due to the high water pressure developed under acceleration. They concluded that the best orientation for the subject was a semirecumbent position with the back elevated 35 degrees from the horizontal. The highest acceleration sustained by the subjects in this study was 14 G, and the end point was not blackout but chest pain of uncertain origin. Also in 1958 Webb and Gray[12] reported the results of tests in an open tank in which the subjects were sitting upright while submerged in water to the eye level. The subjects held their breath during the centrifuge runs. A level of 16 G was attained without blackout. There was no chest pain. The end point was the inability to prevent air from being squeezed from the chest by the increased water pressure even with the mouth taped shut.

Neither of these 1958 studies produced protection greater than the simpler supine support system. However, the cardiovascular system was extremely well protected, and the facilitation of movement by the bouyancy of the water was substantiated.

Description of Water Immersion Capsule

In order to study the principles of water immersion for G protection as proposed by Gray, construction of a capsule which could be mounted on the fifty foot radius human centrifuge at the Aviation Medi-

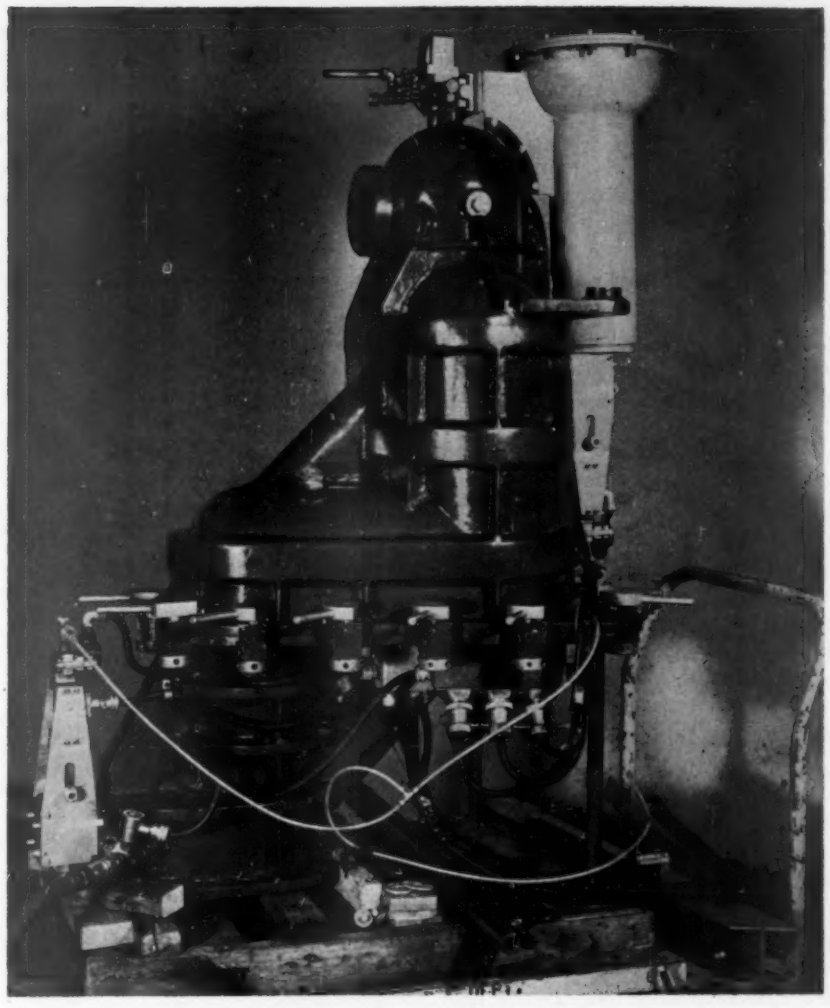


FIG. 1. The total water immersion G-capsule.

cal Acceleration Laboratory, Johnsville, Pennsylvania, was begun in 1957. The capsule (Fig. 1) was made of one-quarter inch aluminum, reinforced to withstand an internal pressure of 100 pounds per square inch with small expansion. The capsule was built in two parts, divided at the seat level. The seal is watertight at 100 pounds per square inch internal pressure. There are five water valves. At the foot of the capsule is a water inlet valve, a water outlet valve and a large emergency dump valve. At the top of the upper section is an overflow valve, and at the back of the upper section is a valve for closing off the standpipe behind the capsule. There are seven watertight openings for the breathing mask hose, microphone connection, and wiring for various signalling and recording devices. In the front of the head section is a plexiglass face plate which can be removed for rapid access to the subject's head.

The capsule was constructed to allow adequate clearance for an average size man, but volume was kept minimal in order to reduce weight. The capsule with its associated hardware weighs 400 pounds.

Breathing Mask: Subjects wore breathing masks specially designed and constructed to be pliable and yet resist gross deformations under the pressures expected during the experiment. The single hose from the mask to the outside of the capsule had to be of sufficient diameter to allow free flow of air, but not so large as to create an unacceptable dead space. Incorporated in the breathing mask was a microphone for the subject, and a loud-speaker was mounted externally on the capsule next to the head section. These provided two-way communication between the subject and the project coordinator.

Signalling Devices: The subject was provided with hand signalling devices. One finger control was a "dead man switch" which the subject was required to hold closed against spring pressure from the beginning of the count-down to the end of the centrifuge run. Releasing this switch would terminate the run. Another control was the emergency dump switch. Pressing this switch would cause termination of the run and dumping of water which would empty the head area within three seconds. A third signalling switch was available for the subject to respond to light signals during the runs. Failure to respond to

the light signals within one and one-half seconds would terminate the run.

Spectacles: The eyes were in direct contact with the water in the capsule in order to prevent eye injuries such as were experienced by Stapp in 1951 and 1954.[13] Since water was in direct contact with the cornea, it was necessary to construct a special set of spectacles to enable the subject to see clearly through the plexiglass face plate.

Electrocardiograms: Electrocardiographic leads were run through one of the openings in the capsule. The leads were placed in the midaxillary lines at the level of the apex with the ground over T-10. Standard electrode paste was used. The lead contacts were taped in place and an elastic bandage was wrapped around the chest for additional support and to minimize dispersion of the electrode paste. The electrocardiographic signals were amplified on the centrifuge arm and passed through slip rings to a direct-writing ink recorder in the control room. The physician monitoring the electrocardiogram could terminate the centrifuge run at any time by means of a push button switch.

Respiratory System Pressure: Because degassed water was not used in the capsule, gas bubbles formed and under acceleration these bubbles moved toward the back of the capsule to form an air pocket which would permit water to compress the chest (diver's squeeze). In order to keep the chest volume change minimal, it was deemed advisable to provide extra intrathoracic pressure. A compressed breathing air source was used. The air passed through a reduction valve and was finally supplied to the subject through a G-activated valve which regulated the respiratory system pressure at approximately one pound per square inch over ambient air pressure for each $4^1/_2$ G. As the centrifuge speed increased, the respiratory system pressure smoothly rose to a value determined by the peak G, then smoothly returned to ambient pressure as the centrifuge came to a stop. This system was expected not only to minimize the chest compression but also to help maintain adequate blood oxygenation by increasing the partial pressure of the alveolar oxygen.

Experimental Procedure

Three volunteer subjects were utilized in this study. Their ages were thirty-five, thirty-three and thirty-nine years, respectively. They were normal healthy males. All were experienced centrifuge subjects.

Before each series of runs the subject was given a general physical examination. A clinical electrocardiogram was taken. The subject, dressed in swimming trunks, then sat on the lower half of the capsule. The electrocardiographic leads, breathing masks, spectacles and hand switches were put on and adjusted. The upper half of the capsule was then lowered into place and tightened. After all communications, monitoring devices and valves were given a functional check, the capsule was completely filled with water at a temperature of approximately 95°F. All air bubbles were worked to the top of the capsule by the subject and allowed to escape through the overflow valve which was then closed. The water in the standpipe in the back of the capsule was reduced in level until the subject stated that breathing was eupneic. A final briefing was given by the coordinator, and the final ten second count-down was begun, at which time the subject held the "dead man" switch closed and began responding to the signals. At the count of eight, the valve in the standpipe was closed and all valves were locked electrically. At the count of ten the centrifuge run began.

The centrifuge runs were twenty-five seconds in length, with the acceleration pattern having a versine wave form (normal distribution curve). At the end of a run the valve in the standpipe was opened, permitting the subject to breathe. The subject was questioned concerning his condition. If all was well, a twenty-minute waiting period was allowed before the next run was made. A maximum of four runs was made during any one morning or afternoon. When the subject left the capsule, he was examined clinically.

Results

Subject 1: The first subject's initial run was at a peak of 4 G. Exposures to new levels of acceleration stress for this subject were limited increments of 2 G over the highest level previously experienced. At 24 G the subject noted frontal sinus pain. This was more severe at 26 G and a few flecks of blood were blown from the nose after the run. Shortly after the 26 G run, the subject also noted pain in the left great toe which lasted several days. Three days later the subject was exposed to 28 G and experienced very severe, knifelike frontal sinus pain during the middle and latter portions of the run. He was found to have a barotraumatic type of sinusitis, with drainage of blood from the frontal sinus for approximately two weeks following the 28 G run.

In order to prevent water from leaking into the mask under acceleration, it was necessary to cinch the mask against the face as tightly as possible. This was uncomfortable. A rhinorrhea occurred with copious secretions. The sinusitis was believed to be due, in part at least, to the inability to equalize the pressures between the frontal sinuses and the rest of the respiratory system. This subject also occasionally experienced abdominal pain during the run.

Subject 2: Because of the above sinus and ear problems, pressurized breathing was not used for subjects 2 and 3. Instead, intratho-

racic pressure was maintained at 1 atmosphere by simply leaving the breathing tube open to the outside air.

The second subject successfully sustained 26 G. At that point he did not wish to continue as a subject due to apprehension which was manifested as a decrease in breath-holding ability. He also noted abdominal pain but found that he could eliminate the pain by tightening of the abdominal musculature.

Subject 3: The third subject reached 31 G. Following the 31 G run, he repeated the 31 G exposure with the peak acceleration maintained for a period of five seconds. He had a slight frontal sinus pain during the peak acceleration and noted a few flecks of blood in his handkerchief the following morning. This subject routinely experienced abdominal pain at all acceleration levels above 10 G. He found that he could always eliminate this pain by tightening the abdominal muscles but he had to strain harder with increasing G levels.

The positive findings on examination following the centrifuge runs were slight disturbances in equilibrium in all subjects following the higher G runs; a few petechiae on the nose and lips of all subjects; a barotraumatic type of sinusitis in the first subject; pain in the left great toe of the first subject, possibly due to a small embolus, following a 26 G run.

The negative findings are quite important. There was no grayout, blackout or unconsciousness which indicated that circulation through the eyes and brain was maintained. The only electrocardiographic change which occurred was a slight sinus bradycardia during the acceleration. There were no arrhythmias, and the postrun electrocardiograms revealed no changes from the prerun tracings. There was no chest pain, cough or signs of congestion during the postrun examination. The superficial vessels showed no signs of distention. The subjects were usually not excessively fatigued. The blood pressure determinations were within normal limits of variation following the runs. The tympanic membranes and the eye grounds were normal except in one case in which redness occurred along the handle of the malleolus and over the pars flaccida. There was no pain in the eyes during the runs. Urinalyses failed to reveal any significant abnormalities. Finally, there was no demonstrable decrement in the performance of a simple task or in the ability to move at accelerations as high as 31 G.

Comments

The results of these experiments indicate that a closed water immersion system gives excellent protection against the effects of acceleration on the cardiovascular system of subjects in the prone position. The complete absence of any evidence of pooling in the extremities shows that the theoretic basis for this system is valid. This substantiates in humans the results of Morris et al.[14] who exposed guppies while submerged to 50 G with the only evidence of dysfunction being that the fish swam on their sides for fifteen minutes after the centrifuge exposures.

Except for the disturbance in equilibrium, the difficulties encountered in this experiment originated in the gas-filled spaces. It was expected that such might be the case. As noted previously, in gas-filled spaces the gradient of fluid pressure external to such a space is opposed by a single gas pressure. On a mechanical basis it is obvious that the pressure of the gas within such a space would be, at best, only an average of the pressure gradient external to the space. The only place where the air pressure and the opposing fluid pressure would be equal would be a plane at about the midpoint of the greatest dimension of the space perpendicular to the axis of the resultant acceleration vector. Above this plane the fluid pressure would be less than the air pressure; below this plane the fluid pressure would be greater than the air pressure.

Since most of the work of respiration is done by the lower respiratory system, it would appear necessary that the water pressure to be matched in order to achieve eupnea would be at some level on the chest. However, experiments conducted by Paton and Sands[15] using human subjects revealed that eupnea occurred when the plane of equal pressure was higher at the suprasternal notch. These findings were substantiated by the use of an aqualung and also in the "G capsule." In this device, breathing was most comfortable when water in the standpipe was at approximately chin level. We, like Paton and Sands, are unable to offer a satisfactory explanation as to why 65 to 75 per cent of the height of the respiratory system should be below the eupneic pressure level.

The position to which the plane of equal pressures in the respiratory system shifted as a result of changing "up" from the top of the head to the back during the centrifuge runs is unknown. Such information is necessary for

a better understanding of the reasons for the success of this experiment.

Possible Dangers of Experiments: There are obvious dangers to human subjects in conducting experiments of this type. One such danger is suggested by what was probably an embolic phenomenon in subject 1. When the anatomic relationships of the ostia of major vessels branching from the aorta are considered in conjunction with the changing acceleration vector, it is altogether reasonable to suggest that a small air bubble entering the pulmonary circulation due to a subclinical lung tissue rupture could have reached the toe.

Another unknown quantity is the pressures within the vessels in the chest. What is their magnitude under acceleration, and how much do they exceed air pressure? At what acceleration can rupture be expected? Many of these questions can be answered only by experiments with instrumented animals. Such experiments are necessary before proceeding further with human subjects in attempting higher accelerations, in longer exposures to those accelerations already experienced or in a different acceleration vector.

The frontal sinus hemorrhage in the first subject was not predicted but had been considered as a possibility. As noted previously, this was considered to be due to excessive fluid pressure caused by the increased respiratory system pressure. The occurrence of frontal sinus pain in subject 3 suggests that frontal sinus bleeding will determine tolerance to acceleration in the prone position in a water protection system.

Conclusions

1. A closed water system for the protection of the cardiovascular system of human centrifuge subjects in the prone position offers protection superior to any other system.

2. An additional benefit of a complete water immersion protection system is the buoyancy of the body by the water, which permits easy movement and use of the extremities during high acceleration exposures.

3. The end point for acceleration tolerance in this system in the prone position may be frontal sinus pain.

4. Animal experimentation is necessary before further evaluation of the system is conducted with human subjects.

Summary

A closed water immersion system for the protection of the cardiovascular systems of human centrifuge subjects against the effects of acceleration is described. One subject was exposed to accelerations as high as 31 G. The first subject had frontal sinus hemorrhage at 28 G, possibly due to high respiratory system pressure used to protect the chest but which was later found to be unnecessary. The second subject stopped at 26 G due to anxiety. The third subject successfully sustained a 31 G exposure for 5 seconds without injury. The only clearcut evidence of cardiovascular system dysfunction was frontal sinus hemorrhage. An additional advantage of the system was found to be that movement of the extremities during high accelerations was not hindered.

References

1. Duane, T. D. Preliminary investigation into the study of the fundus oculi of human subjects under positive acceleration. Aviation Medical Acceleration Laboratory, Report NADC-MA-5303. U. S. Naval Air Development Center, Johnsville, Pa., July 1, 1953.
2. Duane, T. D., Ziegler, J. E. and Hunter, H. Human tolerance to combined acceleration. Aviation Medical Acceleration Laboratory, Report NADC-MA-L5207. U. S. Naval Air Development Center, Johnsville, Pa., 1952.
3. Webb, M. G. Some effects of acceleration on human subjects. *J. Aviation Med.*, 29: 879, 1958.
4. Zuidema, G. D., Cohen, S. I., Silverman, A. J. and Riley, M. B. Human tolerance to prolonged acceleration. *J. Aviation Med.*, 27: 469, 1956.
5. Bühlen, L. Versuch über die Bedeutung der Richtung beim Einwirken von Fleihkräften auf den menschlichen Korper. *Luft fahrtmedizen*, 1: 307, 1937.
6. Gray, R. F. and Collins, C. C. Pilot performance and tolerance studies of orbital re-entry acceleration. Aviation Medical Acceleration Laboratory, Letter Report TED ADC AE-1412, Ser. 7186. U. S. Naval Air Development Center, Johnsville, Pa., Sept. 19, 1959.
7. Clarke, N. P., Hyde, A. S., Cherniak, N. S. and Lindberg, E. F. A preliminary report of human response to rearward-facing reentry accelerations. Wright Air Development Center, WADC Technical Note 59-109. Dayton, Ohio, July, 1959.
8. Gray, R. F. Mechanical systems suggested for G protection. Aviation Medical Acceleration Laboratory, Report NADC-MA-5708. U. S. Naval Air Development Center, Johnsville, Pa., July 15, 1957.
9. Gauer, O. The physiological effects of prolonged acceleration. In: German Aviation Medicine in World War II, vol. I, p. 582. U. S. Government Printing Office, Washington 25, D. C., 1950.
10. Wood, E. H., Code, C. F. and Baldes, E. J. The

protection afforded the human by hydrostatic, as compared to pneumatic, anti-G devices. National Research Council Committee on Aviation Medicine, Report No. 207. Rochester, Minn., Acceleration Laboratory, Mayo Aero Medical Unit, 1943.

11. BONDURANT, S., BLANCHARD, W. G., CLARKE, N. P. and MOORE, F. Effect of water immersion on human tolerance to forward and backward acceleration. *Aerospace Med.*, 29: 872, 1958.
12. WEBB, M. G. and GRAY, R. F. Human tolerance to high acceleration stress (Mayo tank). Aviation Medical Acceleration Laboratory, Letter Report TED ADC AE 1411, Ser. 3535. U. S. Naval Air Development Center, Johnsville, Pa. May 2, 1958.
13. STAPP, J. P. Effects of mechanical force on living tissues. I. Abrupt deceleration and windlbast. *J. Aviation Med.*, 26: 268, 1955.
14. MORRIS, D. P., BEISCHER, D. E. and ZARRIELLO, J. J. Studies on the G tolerance of invertebrates and small vertebrates while immersed. *J. Aviation Med.*, 29: 438, 1958.
15. PATON, W. D. M. and SANDS, A. Optimum intrapulmonary pressure in underwater respiration. *J. Physiol.*, 106: 119, 1947.

Review

Four Decades of Diuretic Therapy

A Review of Its Progress and Present Status*

ALFRED VOGL, M.D., F.A.C.C.

New York, New York

THE 16th of October 1919, may be called the birthday of modern diuretic therapy. It was the day on which a sudden rise in urinary output was noticed in a nonedematous girl who that same morning had received an injection of an antisyphilitic organomercurial, Novasurol®.[1] The great impact which the amazing diuretic potency of this drug had upon treatment of edema and its rapid and universal acceptance can be understood best if one realizes that at that time the standard diuretic was theobromine sodium salicylate, a preparation that had owed its popularity certainly not to its spectacular effectiveness but rather to its persuasive trade name, Diuretin.

During the subsequent thirty years not very much was added to our initial notions concerning dosage, indications and contraindications for the use of organomercurials as diuretics.[2] This period was, however, immensely productive in clarifying the physiology and pharmacology of diuresis and diuretics, an area of research for which the mercurials served as a uniquely suitable tool. Due to their potency and low toxicity the field of diuretics was dominated in this era by the mercurials to the practical exclusion of previously used diuretics and other time-honored measures. This, in turn, caused excesses in their use by some enthusiasts and the widely held impression that all was lost when an edematous patient failed to respond to a mercurial. Ten years ago it seemed necessary to denounce this monopoly and re-emphasize the merits of nonmercurial diuretics and other effective measures.[2]

During the past decade this situation has unexpectedly but radically changed. Today nonmercurial diuretics dominate the scene. What has happened during recent years to reshape the methods of treatment for the edematous patient so thoroughly? The following events were largely responsible for this development:

1. The importance of sodium restriction in all situations associated with generalized edema has been generally recognized.
2. The role of hormonal agents in the production of edema has been established.
3. The profound influence of diuretic treatment upon the course of congestive heart failure has been clarified, in contrast to its purely symptomatic effect in renal, hepatic, hypoproteinemic and hormonal edema.[3]
4. The causative relationships of the so-called "low salt syndromes" to therapeutic measures (drugs and diet) on one hand and the history of the disease on the other have become better understood.
5. New potent nonmercurial diuretics, suitable for oral administration, have been introduced.

Where does all this leave the organomercurials in the medical practice of today? Have they become obsolete?

MERCURIAL DIURETICS

Indications: Scrutiny of the experience accumulated today indicates that mercurials are still the most potent, uniformly effective and dependable diuretic drugs available. Because of these properties and their low toxicity they remain the diuretics of choice when a prompt and copious diuretic response is needed as in: (1) acute left ventricular failure with severe

* From the Medical Department, New York University, Bellevue Medical Center, New York, New York.

pulmonary congestion; (2) far advanced congestive heart failure; (3) congestive failure progressing despite other measures; (4) for purposes of therapeutic testing (particularly for the differentiation of the symptoms of left ventricular failure from those of angina pectoris or bronchial asthma).[4] In all these circumstances a mercurial can generally be relied upon to perform as expected.

Contraindications: The contraindications to the use of mercurials have been redefined with advancing experience and can now be limited to the following: (1) hypersensitivity to the compound in use (usually permitting a change-over to a different mercurial compound); (2) failure of preceding mercurial injections to produce significant diuresis on two successive occasions; (3) advanced renal insufficiency: (4) marked edema in the gluteal region (precluding intramuscular injection at this site and necessitating administration either intravenously or in a nonedematous part subcutaneously).

Nonmercurial Diuretics

What has become of the nonmercurial diuretics that have enjoyed some popularity in recent years?

Exchange Resins: The introduction of the cation exchange resins was greeted with great expectations as they seemed to hold up to the patient the *fata morgana* of tasty food from which the noxious sodium could be removed surreptitiously after he had enjoyed his meal. However, because of their bulk, sand-like consistency and various side effects they have never been widely used and have in clinical practice almost fallen into oblivion by now.

Xanthine and Amino-uracil Compounds: Some more recently introduced xanthine compounds and the related amino-uracils have not provided major advantages over earlier preparations, especially the long popular aminophylline. The search for a parenteral preparation in this group that could be potent but painless on intramuscular injection has so far been unsuccessful.

One of the newer amino-uracil or pyrimidine diuretics is amino-iso-metadrine (Rolicton®). This drug may be of interest in the treatment of patients in whom maintaining potassium balance is difficult.[5] Rolicton at a dosage of 1,200 mg. a day has been shown to have a definite though moderate diuretic effect without excessive potassium loss. Unlike the xanthines, the amino-uracils do not increase cardiac output, but they share with them an early development of tolerance.

Osmotic Diuretics: The osmotic diuretics have not fared any better. Even though the assumption that they produced essentially water diuresis has proved to be erroneous (they do cause increased natriuresis), they are of little value in actual practice.[6] Their diuretic effect is modest, parenteral administration is cumbersome and infusions of hyperosmotic solutions of mannitol or sorbitol are not without danger.

Carbonic Anhydrase Inhibitors: The introduction of acetazolamide (Diamox®) and subsequently ethoxzolamide (Cardrase®) which were believed to act through their inhibitory activity on renal carbonic anhydrase, represented the first great breakthrough in diuretic therapy in recent years. The practical importance of these drugs is based upon their oral effectiveness and ability to induce predominant natriuresis. Their disadvantages were a comparatively low potency, disproportionately high concomitant potassium excretion, production of metabolic acidosis, failure to increase the diuretic effect by increasing the dosage beyond a certain point, rapid development of tolerance and various side effects (related either to their inherent sulfonamide nature or their inhibitory effects on extrarenal carbonic anhydrase).

Thiazide Diuretics

The research that led to the synthesis of acetazolamide marked the beginning of the production of a series of other diuretic sulfonamide derivatives. It culminated in the creation of thiazide diuretics: first, chlorothiazide (Diuril®) and subsequently hydrochlorothiazide (Hydrodiuril®, Esidrix®), flumethiazide (Ademol®, Saluretin®), hydroflumethiazide (Saluron®) and benzydroflumethiazide (Naturetin®). These compounds generally proved to be of outstanding diuretic potency, of low toxicity and, contrary to expectations, of low activity only as carbonic anhydrase inhibitors. Their mechanism of action remains unexplained. Their important common properties are oral effectiveness approximating, in larger doses, that of parenteral mercurials; prompt onset of diuresis which lasts from eight to twelve hours; an almost equal action upon excretion of sodium and chloride (thus reducing the tendency to alkalosis existing with mercurials and to acidosis occurring with acetazolamide); a tendency to relatively

high excretion of potassium (less apparently than with acetazolamide but more than with mercurials); diuretic effectiveness even on continuous use (in contrast to the quick development of tolerance during acetazolamide treatment); and a low incidence of significant side effects (if hypokalemia is forestalled by appropriate measures).[7]

Side Effects: The side effects encountered with the use of thiazide compounds are those known to occur either with other carbonic anhydrase inhibitors (paresthesias, drowsiness) or other sulfonamide derivatives (skin rashes,[8] agranulocytosis,[9] thrombocytopenic purpura,[10,11] crystalluria).[12] The occurrence of acute pancreatitis[13] and jaundice of the intrahepatic cholestasis[14] type has been attributed to the use of chlorothiazide. These drugs have in some patients produced photosensitivity resulting in rashes in the exposed areas of the skin.[15] A tendency to increased levels of serum uric acid, probably due to a depression of renal uric acid excretion, has been observed with the prolonged intake of chlorothiazide.[16–18] This does not generally lead to any symptoms except in patients with a gouty diathesis in whom clinical gout may develop.[19,20] In a few patients with renal insufficiency treated for edema with chlorothiazide, the syndrome of "salt-losing nephritis" has been seen to develop.

Because tolerance does not develop easily and the "saluretic" effect of the thiazide diuretics thus can continue indefinitely, their prolonged and uninterrupted use is fraught with the risk of hypokalemia as the result of continuous excessive potassium loss. This may produce no more than a feeling of undue fatigue but it has led to muscle paralysis[21] and, especially in elderly people taking digitalis, to very disturbing arrhythmias. On the other hand, the production of hypokalemia has been used successfully in the treatment of heart block with recurrent Stokes-Adams attacks.[22]

Occasionally the continued salt loss during protracted thiazide diuresis has led to hypochloremic alkalosis with or without associated hypokalemia, requiring withdrawal of the drug and electrolyte replacements.[23–25] Patients with cirrhosis of the liver who respond well to thiazide diuretics show a pronounced tendency to excessive potassium loss, associated with an elevation in serum ammonia concentration and symptoms of progression toward hepatic coma.[26,27] Potassium supplements could not prevent this development while restricted protein intake and use of antibiotics (which suppress urea producing bacterial activity) appeared more beneficial.[24,25,28]

Dosage: The possibility of these complications must be remembered if thiazide diuretics are to be used with a minimum of side effects. Potassium deficiency, in particular, may manifest itself by symptoms which may easily be missed as such and attributed instead to the basic cardiac or renal disease. For maintenance thiazide medication it is probably safest to use repeated short courses (e.g., four days a week with three day intervals, or two day courses with two day intervals), individualizing the dosage by keeping it at the minimum needed for the desired steady diuresis. This daily dosage is usually 500 to 1,000 mg. of Diuril, 50 to 100 mg. of Hydrodiuril or Esidrix, or 5 to 10 mg. of Naturetin, together with 1 to 3 gm. of potassium chloride and orange juice daily.

In acute or severe congestive heart failure it is probably wise to start with a mercurial, although a large dose of a thiazide diuretic (e.g., 2,000 mg. of Diuril or 20 mg. of Naturetin) may be quite adequate for this purpose in many cases. Administration of the required amount in two divided doses, with a six to eight hour interval, appears preferable.[29]

The newest thiazide compounds which are effective in daily doses of 5 to 50 mg. may have the advantage of causing less frequently or severely those side effects which are inherent in their nature as sulfonamide derivatives and carbonic anhydrase inhibitors. They also have occasionally been effective in patients in whom other thiazides had been inadequate or had lost their initial efficacy. Concerning their capacity for producing hypokalemia, however, there is no convincing evidence of their superiority.

TRIAZINE DIURETICS

Of the little known group of formoguanamine or triazine diuretics the recently introduced Chlorazinil® (also known as Daquin or Orpidon in Europe) deserves mention.[30,31] In doses of 300 to 600 mg. per day it can produce marked diuresis with a low urine solute concentration; in other words it promotes water excretion predominantly. This is a property to be kept in mind when faced with the problem of refractory edema associated with low serum sodium concentrations ("dilution hyponatremia"). Together with a restricted water

intake, Rolicton may conceivably aid in restoring electrolyte balance in such circumstances. The fact, however, that hyponatremia is found especially in patients with renal disease, may limit the usefulness of the drug since it tends to impair glomerular filtration, causing a rise in blood urea nitrogen.[30]

Aldosterone-Antagonists

A new and fascinating prospect in diuretic therapy has opened up with the introduction of the aldosterone-antagonists (aldosterone blocking agents).[32] This quite revolutionary advent originated from the recognition of the role mineralocorticoids play in tubular sodium and chloride reabsorption, and from the isolation of aldosterone as the most potent sodium-retaining steroid. It may be recalled here that aldosterone as such does not cause formation of edema. However, in congestive heart failure, cirrhosis or nephrosis aldosterone production is increased, apparently due to a fall in "effective arterial blood volume." The glomerulotubular imbalance associated with these disorders is thereby raised sufficiently to bring about edema. Certain synthetic steroids,[19] spirolactones, have been found to compete with aldosterone at the renal tubular cells. In this way they counteract all its effects, presumably by saturating the binding site in the distal convoluted tubule. Thus, while aldosterone promotes sodium retention, potassium loss and reduction in urinary volume, the spirolactones induce sodium loss, potassium retention and an increase in urinary volume. They are, therefore, unique among diuretic agents in their capacity for preserving potassium while promoting diuresis and natruresis.[33,34]

Limitations: How close do the spirolactones then come to the long awaited "ideal diuretic?" Experience is still rather small. Some known facts, however, indicate certain limitations:

1. The spirolactones cause diuresis and natriuresis only in the presence of increased aldosterone production. (They have no diuretic effect in a nonedematous person in contrast to other diuretic agents.)

2. They do not suppress the formation of aldosterone by the adrenals, but compete with it at the effector organ. Therefore, as continued administration of spirolactones leads to continued sodium loss, the resulting reduction in sodium stores in the body stimulates the adrenals to produce more aldosterone.[35] A vicious cycle may thus become perpetuated.

Indications: Under these circumstances the greatest benefit can be expected from the spirolactones when used in short courses for patients with refractory edema, particularly for those in whom potassium deficiency poses an added problem. Under such circumstances they could reverse the potassium loss while promoting continued sodium excretion. If this action can be maintained until the electrolyte status is improved to a degree that permits the vigorous use of the conventional diuretics again, the spirolactones will fill an urgent need in diuretic therapy. An orally effective spirolactone, Aldactone®, has recently become commercially available in tablets of 100 mg. The effective dosage range has been established at 300 to 1,200 mg. daily. The only side effects reported so far have been occasional drowsiness and skin rashes.

Principles and Technics of Diuretic Therapy

The number of available potent diuretic drugs, discussed previously, is thus quite impressive. Has their introduction changed the principles and technics of diuretic practice? Actually, the basic rules for the management of edematous conditions are still maintained:[4]

1. The underlying disorder must be treated as systematically as possible. In attempting full digitalization, however, it should be realized that some decompensated patients, especially the elderly, are too sensitive to the drug and others who suffer from conditions such as acute myocarditis, pericardial constriction, hyperthyroidism, or mitral stenosis with regular cardiac rhythm may derive no benefit from digitalis. These patients depend largely on effective diuretic treatment.

2. Dietary sodium restriction is imperative in all cases but should be adjusted to the needs of the individual patient. However, to advocate the return to an unrestricted salt diet balanced by a liberal use of diuretics would be a step backward and even more deplorable since the public is just beginning to accept the need for low salt diets in persons with heart failure.

3. Elimination of the intake of chemicals with antidiuretic action must be thorough. The most important of these are the sodium-containing household remedies and food additives; however, the antidiuretic potentialities of other drugs should not be overlooked particularly of phenylbutazone, rauwolfia preparations, narcotics (opiates as well as synthetic

compounds) and finally, mineralocorticoids, androgens and estrogens in higher dosage.

While the general rules for diuretic therapy have thus remained the same, diuretic drug therapy has changed radically during the past decade. The intense but short-lived effects of injected mercurials, with inevitable fluctuations between copious diuresis and fluid retention, have now been generally replaced by methods permitting much smoother therapeutic diuresis. On the other hand, while significant potassium losses were encountered only with excessively large or frequent mercurial diuresis, this problem has become ubiquitous now. With continous use of thiazide diuretics potassium deficiency may develop even without excessive diuresis. Concern about possible potassium imbalance during thiazide diuresis has thus largely supplanted our previous concern with chloride loss during mercurial diuresis. By the same token, prophylactic ammonium chloride medication has been replaced by potassium chloride supplements.

Experience with the newest oral diuretics has, as a whole, been most satisfactory. Together with the organomercurials they have materially contributed to reducing the incidence of "intractable edema." If such a situation is encountered, however, it becomes necessary to combine various diuretic regimens in order to overcome the particular difficulties in a given case.

METHODS TO POTENTIATE DIURESIS

1. Of the older technics of re-enforcing mercurial diuresis, the following two are always worth trying:

(*a*) *Acidification* with ammonium chloride *prior to a mercurial* injection (its potentiating action has been shown to be due to acidification at the tubular epithelial cells rather than to the supply of additional chloride).[36]

In order to avoid possible ammonia intoxication from large doses of ammonium chloride, *l-lysine monohydrochloride* has recently been recommended as a source of chloride.[37] Oral administration of 20 gm. (in four doses of 5 gm. each, in chilled fruit juice after meals) produced a significant rise of the serum chloride in patients with hypochloremic alkalosis. Diuresis was obtained with l-lysine monohydrochloride at this dosage in a majority of mercury-refractory edematous patients. In seven of forty patients, however, gastrointestinal disturbances developed during the medication.

(*b*) *Combination* of each *mercurial* injection with several *aminophylline* injections often succeeds in reviving failing diuresis.[38]

2. *Combining mercurial injections with* three to four day courses of a *thiazide* has produced adequate diuresis when each of these agents alone was ineffective. While thiazide medication *following* the mercurial injection has decidedly a potentiating effect, reversal of the procedure may be ineffective.[39] Occasionally changing from one thiazide to another may restore effective diuresis.

3. *The induction of hyperchloremic acidosis* by means of large doses of acetazolamide and ammonium chloride for several days prior to a mercurial injection is, no doubt, effective in some refractory cases, whether serum chloride is normal or low at the starting point of this procedure.[40] For patients with cirrhosis and advanced edema, calcium chloride[41] or l-lysine monohydrochloride[37] is recommended instead of ammonium chloride to avoid the danger of ammonia poisoning which large doses of ammonium salts are likely to cause in the presence of hepatic insufficiency.[41] This plan is not feasible without some added discomfort, possibly not even without some risk for the patient and, therefore, will be limited to situations in which simpler technics have failed.

4. *Phlebotomy:* In patients in whom hypervolemia, marked by systemic venous engorgement, is a conspicuous feature, reduction of the circulatory blood volume by a sizable phlebotomy can sometimes restore the response to a subsequently administered diuretic.[42]

5. *Steroids:* A regimen that can be decisively helpful in desperate situations is the *introduction of glucocorticoids* into a diuretic program.[43–45] Most workers have used prednisone for this purpose.[46,47] The diuretic action of some corticosteroids was first noticed accidentally when they were used for other indications in patients with edema. Clinical experience has shown that these compounds as such do not generally act as diuretics in congestive failure,[46] but they can revive the response to mercurials and thiazides in some refractory cases. The mechanism through which they act is obscure but it appears most plausible that they either counteract the secondary hyperaldosteronism present in advanced cardiac edema[46] or correct adrenal cortical insufficiency possibly associated with advanced congestive failure.[48] A contributory factor may be an increase in

glomerular filtration which recently was shown to occur under the influence of glucosteroids.

For the purpose of augmenting diuresis, small doses of prednisone are recommended. The effectiveness of the procedure must be tested after about a week of medication by then giving a mercurial or a thiazide diuretic. If diuresis ensues, the steroids should be continued indefinitely at the minimum effective dosage level as long as diuretic treatment is needed. If diuresis does not occur in this way, the steroids are stopped. In practice the procedure is used in the following way: the previous regimen of rest, sodium restriction and digitalization is continued without change. Prednisone is added in doses of 2.5 mg. three times a day. After five to eight days a test dose of a potent diuretic is given. If there is good diuresis, prednisone is continued at the same dosage or, as the condition improves subsequently, at a lower dosage. If no satisfactory diuresis is achieved at the initial dosage, prednisone is tentatively increased to 5 mg. three times a day for a few days, after which the diuretic test dose is repeated. If this fails, the steroids are discontinued.

6. The newest diuretics, the *aldosterone antagonists*, are eminently suited for the potentiation of a diuretic regimen in refractory cases, because they act through mechanisms not utilized previously by other types of diuretics, namely, by inhibiting sodium and chloride reabsorption in the *distal* convoluted tubule. By blocking the action of aldosterone at this level, they also offset potassium loss if caused by previously used diuretics.

A rational schedule for the use of aldosterone blocking agents is the following: the previous diuretic regimen remains in force. Spironolactone (Aldactone) is then added, initially in a dosage of 400 mg., i.e., one 100 mg. tablet four times daily, for five days. The effective dose may lie between 300 and 800 mg. per day. If satisfactory diuresis is produced in this way, the spirolactone may be continued for another five days. Due to the synergism between the older diuretics and spirolactones, significant potentiation of the previously used diuretic regimen can be expected. The increased sodium excretion may increase pre-existent hyponatremia. Hyperkalemia, however, is not likely to be produced except possibly in an occasional case of renal insufficiency.

The methods of diuretic treatment discussed previously offer a great variety of approaches with an excellent chance of success even in obstinate cases of edema. We no longer attempt to produce spectacular diuresis and record weight loss. The lessons of the serious sequelae of excessive diuresis have been learned by now.[4] Gradual removal of edema has been recognized as the best safeguard against the acute "low salt syndromes," especially acute hypokalemia and dehydration. The deliberate restoration of a near physiologic body fluid volume, distribution and electrolyte concentration and subsequent steady maintenance of this status have become the accepted goals of diuretic therapy.[3]

The progress in diuretic therapy has been spectacular in these last four decades. At the same time the multitude, complex variety and remarkable potency of the available diuretic agents have burdened the physician with a difficult task and great responsibility in carrying out a medically sound and carefully individualized therapeutic program. The fight against "intractable edema" has been remarkably successful during the era of modern diuretic therapy. If the new weapons at our disposal now are utilized fully and wisely, the boundaries of truly refractory edema should be pushed back further in great strides.

References

1. Vogl, A. The discovery of the mercurial diuretics. *Am. Heart J.*, 39: 881, 1950.
2. Vogl, A. Thirty years of mercurial diuretics. *M. Rec.*, 163: 189, 1950.
3. Vogl, A. Ueber Ziel und Grenzen diuretischer Therapie. *Wien. klin. Wchnschr.*, 67: 652, 1955.
4. Vogl, A. Diuretic Therapy. The Pharmacology of Diuretic Agents and the Clinical Management of the Edematous Patient. Baltimore, 1953. Williams & Wilkins Co.
5. Platts, M. M. Aminometadrine (Rolicton) in treatment of congestive heart failure. *Brit. Heart J.*, 21: 249, 1959.
6. Bernstein, L. W. et al. Osmotic diuretic treatment of refractory edema. *Circulation*, 17: 1013, 1958.
7. Vogl, A. The low-salt syndromes in congestive heart failure. *Am. J. Cardiol.*, 3: 192, 1959.
8. Keyes, J. W. and Berlacher, F. J. Chlorothiazide. *J. A. M. A.*, 169: 109, 1959.
9. Zuckerman, A. J. and Chazan, A. A. Agranulocytosis following chlorothiazide. *Brit. M. J.*, 2: 1338, 1958.
10. Jaffe, M. O. and Kierland, R. R. Purpura due to chlorothiazide. *J. A. M. A.*, 168: 2264, 1958.
11. Nordquist, P. et al. Thrombocytopenia during chlorothiazide treatment. *Lancet*, 1: 271, 1959.
12. Yates-Bell, J. G. Renal colic and anuria from acetazoleamide (Diamox). *Brit. M. J.*, 2: 1392, 1958.

13. Johnston, D. H. and Cornish, A. L. Acute pancreatitis in patients receiving chlorothiazide. *J. A. M. A.*, 170: 2054, 1959.
14. Drerup, A. L. et al. Jaundice occurring in patients treated with chlorothiazide. *New England J. Med.*, 259: 534, 1958.
15. Harber, L. C. et al. Photosensitivity due to chlorothiazide and hydrochlorothiazide. *New England J. Med.*, 261: 1378, 1959.
16. Laragh, J. H. et al. Effect of chlorothiazide on electrolyte transport in man. *J. A. M. A.*, 166: 154, 1958.
17. Monroe, K. E. et al. Effect of chlorothiazide therapy on serum uric acid and uric acid excretion. *New England J. Med.*, 261: 290, 1959.
18. Oren, B. G. and Belle, M. S. Chlorothiazide as a hyperuricemic agent. *J. A. M. A.*, 168: 2128, 1958.
19. Kadisch, A. H. Correspondence. *J. A. M. A.*, 169: 526, 1959.
20. Warshaw, L. J. Acute attacks of gout precipitated by chlorothiazide-induced diuresis. *J. A. M. A.*, 172: 802, 1960.
21. Cohen, T. Hypokalemic muscle paralysis associated with administration of chlorothiazide. *J. A. M. A.*, 170: 2083, 1959.
22. Tobian, L. 32nd Scientific Session, American Heart Association. *Circulation*, 20: 779, 1959.
23. Castle, C. H. et al. Observations on the diuretic effect of chlorothiazide. *Arch. Int. Med.*, 103: 415, 1959.
24. Dinon, L. R. and Vander Ver, J. B. Clinical experience with chlorothiazide, with particular emphasis on untoward responses. *Am. J. M. Sc.*, 236: 533, 1958.
25. Kirkendall, W. W. Clinical evaluation of chlorothiazide. *Circulation*, 19: 933, 1959.
26. Magid, J. J. et al. Ammonia intoxication in patients with cirrhosis treated with chlorothiazide. *J. A. M. A.*, 168: 35, 1958.
27. Myerson, R. M. et al. Acetazolamide and chlorothiazide in the treatment of ascites due to cirrhosis of the liver. *New England J. Med.*, 260: 28, 1959.
28. Mackie, J. E. et al. Production of impending hepatic coma by chlorothiazide and its prevention by antibiotics. *New England J. Med.*, 259: 1151, 1958.
29. Moyer, J. H. and Fuchs, M. Diuretic therapy in syndromes associated with sodium and water retention. *Am. J. Cardiol.*, 4: 786, 1959.
30. Ford, R. V., Rochelle, J. B., III, Bullock, A. C., Spur, C. L., Handley, C. and Moyer, J. H. Laboratory and clinical observations on chlorazanil, a non-mercurial orally effective diuretic agent. *Am. J. Cardiol.*, 3: 148, 1959.
31. Hirshleifer, I. Water diuresis with minimal electrolyte disturbance (clinical experience with a new triazine compound). *Am. J. Cardiol.*, 3: 162, 1959.
32. Kagawa, C. W., Sturtevant, F. W. and Van Arman, C. J. Pharmacology of a new steroid that blocks salt activity of aldosterone and desoxycorticosterone. *J. Pharmacol. & Exper. Therap.*, 126: 123, 1959.
33. Gantt, C. L. and Dyniewicz, J. Some effects of 17-spirolactosteroids on the edema of cirrhosis, with observations of a new spirolactone derivative. *Clin. Res.*, 7: 294, 1959.
34. Liddle, G. W. Recent advances in the knowledge of the causes of edema and in diuretic therapy: Aldosterone antagonists. *Arch. Int. Med.*, 102: 998, 1958.
35. Leutscher, J. A., Jr. and Lieberman, A. H. Aldosterone. *Arch. Int. Med.*, 102: 314, 1958.
36. Levy, R. I. et al. Effects of acid-base balance on diuresis produced by organic and inorganic mercurials. *J. Clin. Invest.*, 37: 1016, 1958.
37. Brailovsky, D. et al. The use of l-lysine monohydrochloride in the treatment of mercurial resistant edema. *Am. J. M. Sc.*, 238: 287, 1959.
38. Vogl, A. and Esserman, P. Aminophylline as a supplement to mercurial diuretics in intractable congestive heart failure. *J. A. M. A.*, 147: 625, 1951.
39. Ford, R. V. and Rochelle, J. B., III. The differing mechanisms of action of mercurials, carbonic anhydrase inhibitors, and chlorothiazide as diuretic agents. *J. Lab. & Clin. Med.*, 53: 53, 1959.
40. Rubin, A. L. and Braveman, W. S. Treatment of the low salt syndrome in congestive heart failure by the controlled use of mercurial diuretics. *Circulation*, 13: 655, 1956.
41. Hollister, J. H., Lubash, G. D., Cohen, B. D., Braveman, W. S., Rubin, A. L., and Luckey, C. H. Refractory edema treated with calcium chloride in combination with mercurial diuretics. *Am. Heart J.*, 56: 629, 1958.
42. Ray, C. T. Mercurial diuretics. *Arch. Int. Med.*, 102: 1016, 1958.
43. Bickel, G. Action favorable de la prednisone dans certaines insuffisances cardiaques refractoires. *Med. et Hyg.*, 13: 472, 1955.
44. Camara, A. and Schemm, F. Corticortropin in heart disease; its paradoxical effect on sodium excretion in resistant congestive failure. *Circulation*, 11: 702, 1955.
45. Newman, D. A. Reversal of intractable cardiac edema with prednisone. *New York J. Med.*, 59: 625, 1959.
46. Gutner, L. B. et al. The use of prednisone in congestive heart failure. *Am. J. M. Sc.*, 234: 281, 1957.
47. Riemer, A. D. Application of the newer corticosteroids to augment diuresis in congestive heart failure. *Am. J. Cardiol.*, 1: 488, 1958.
48. Mickerson, J. N. and Swale, J. Diuretic effect of steroid therapy in obstinate heart failure. *Brit. M. J.*, 1: 876, 1959.

Report on Therapy

Cardiovascular Effects of Hydroxyzine*

MAX H. WEIL, M.D., PH.D. *and* ROBERT B. SUDRANN, M.D.

Los Angeles, California

HUTCHEON and co-workers[1] demonstrated that hydroxyzine reduces the incidence and duration of ventricular dysrhythmias in cats treated with epinephrine. Clinical trials by Burrell et al.[2] subsequently indicated that hydroxyzine was effective in the treatment of twenty-eight of thirty-three patients with atrial tachycardia, wandering atrial pacemaker, premature ventricular contractions and ventricular tachycardia. Results were less satisfactory in treatment of atrial fibrillation although it was reported that in six of seventeen patients sinus rhythm was restored following administration of hydroxyzine.

The purpose of the present studies was to evaluate the usefulness of hydroxyzine for the treatment of cardiac dysrhythmias. Hemodynamic observations were also made on human subjects who did not have cardiac dysrhythmias to gain additional information on the cardiovascular actions of this drug.

TABLE I

Abnormalities of Rhythm Treated with Hydroxyzine

	No.
Premature ventricular contractions	4
Supraventricular tachycardia	3
Auricular fibrillation	2
Complete A-V block	1
Nodal rhythm	1
Auricular flutter	1
Second Degree A-V block	1
Total	13

MATERIALS AND METHODS

Treatment of Patients with Cardiac Dysrhythmias: Hydroxyzine was used on fourteen occasions in the treatment of twelve patients with acute cardiac dysrhythmias. The abnormalities in cardiac rhythm are indicated in Table I. Hydroxyzine hydrochloride preserved in 0.9 per cent benzyl alcohol diluted to a concentration of 25 mg. per ml. was used.† The drug was injected into an antecubital vein at the rate of 25 mg. per minute. A total dose of 75 mg. was used in most trials. In one instance 37.5 mg. of hydroxyzine was injected directly into the pulmonary artery during cardiac catheterization. Approximately one-half the patients were receiving digitalis. Clinical and electrocardiographic studies were made prior, during and at intervals during the hour following injection of hydroxyzine (Table II).

Hemodynamic Studies: Two patients in whom cardiac catheterization revealed no significant cardiac abnormalities and two hospitalized patients who had recuperated from noncardiac diseases (respiratory infection, duodenal ulcer) served as subjects for this part of the study. In addition, one patient with mitral stenosis of moderate severity was studied. Hydroxyzine was injected into an antecubital vein as described previously. Doses of 75 or 100 mg. were employed. Pressures were measured continuously in the pulmonary artery and right ventricle in two subjects employing conventional catheterization technics. Simultaneously, arterial pressure was measured through a needle inserted into the radial artery. Strain gauge pressure transducers and oscillographic or direct writing recorders were employed. Cardiac output was determined utilizing the indicator dilution technic of Nicholson and Wood[3] modified for use with an oximeter amplifier[4] and indocyanine green dye. Measurements of cardiac output were made during a control period and between two and ten minutes following the injection of hydroxyzine.

* From the Department of Cardiology, City of Hope Medical Center, Duarte, and the Department of Medicine, University of Southern California School of Medicine, Los Angeles, California. Supported by grants-in-aid from the American Heart Association and the Los Angeles County Heart Association.

† Supplied as Atarax by the J. B. Roerig Company, New York, New York. Hydroxyzine pamoate is marketed as Vistaril.

TABLE II
Clinical Observations in Patients with Cardiac Dysrhythmias Treated with Hydroxyzine

Case	Age and Sex	Clinical Features	ECG	Dose (mg. I.V.)	Response	Side Effects	Digitalis	Comments
1	61, M	Supraventricular tachycardia; palpitations for 36 hours	Supraventricular tachycardia	50	None		Yes	
2	64, F	ASHD; carcinoma of cervix	Auricular fibrillation (acute onset)	75	None	Drowsiness; nausea	No	
3	29, F	RHD; acute shortness of breath; palpitations	Supraventricular tachycardia	50	None		No	Prednisolone, 10 mg. t.i.d., Cedilanid (0.3 mg.) abolished tachycardia
4	47, F	RHD; mitral stenosis and insufficiency; tricuspid insufficiency; congestive heart failure; dyspnea, ankle edema, fatigue and chest pain	Multiple PVC's; bigeminal rhythm	75	None	Drowsiness	Yes	Pain in chest for 1 minute during injection
5	50, M	ASHD; myocardial infarction; syncope on exertion	Complete A-V block; idioventricular rhythm	100	None	Somnolent	No	Isoproterenol and prednisolone effective
6	55, F	ASHD; hyperthyroidism; palpitations, dyspnea, ankle edema and cough on exertion	Normal rhythm; old septal infarct	75 50	See comments	Drowsiness	No	Conversion of nodal to sinus rhythm following injection of 25 mg. hydroxyzine, reversion to nodal rhythm 45 minutes later. A second trial employing 50 mg. provided similar response except that sinus rhythm persisted only for 10 minutes; no effect with oral drug
7	50, F	Previous mitral commissurotomy; palpitations, dyspnea	RBBB; atrial fibrillation	75	None	Drowsiness	Yes	
			RBBB; atrial flutter	100	None	Drowsiness	Yes	Ventricular rate reduced to 65, 10 minutes following intramuscular administration of sodium luminal (50 mg.)
8	24, M	Pulmonic stenosis; asymptomatic	Right ventricular hypertrophy; multiple PVC during catheterization	37.5 mg. into pulmonary artery	None		No	PVC's during withdrawal of catheter across pulmonic valve, unaffected by medication
9	7½, F	Eisenmenger's syndrome; cyanosis, tiredness, fainting, secondary polycythemia	Second degree A-V block; Wenkebach phenomenon	75	None	Somnolent (3–4 hours); very bitter taste in mouth	No	
10	80, F	ASHD; anginal pain	LBBB; PVC	75	None	Drowsiness	Yes	
11	25, F	Atrial septal defect; palpitations	Supraventricular tachycardia	75	None	Drowsiness	Yes	
12	37, M	Duodenal ulcer; anxiety tension state; abdominal pain; sweating; insomnia	Multiple PVC	75	None	Drowsiness	No	

In three subjects two or three additional measurements were made at approximately ten minute intervals.

RESULTS

Treatment of Cardiac Dysrhythmias: Hydroxyzine failed to produce significant change in cardiac rhythm in eleven of twelve patients with cardiac dysrhythmia (Table II). In one patient who had thyrotoxic and arteriosclerotic heart disease, nodal rhythm was converted to regular sinus rhythm. However, this conversion could not be sustained for more than forty-five minutes following injection. In the same patient, oral medication using generous doses was ineffective. No patient demonstrated a significant change in heart rate or blood pressure. Sedation with drowsiness and somnolence were immediate and prominent after intravenous injection of hydroxyzine in the

TABLE III

Average Values of Cardiac Output, Heart Rate and Mean Arterial Pressure Two to Ten Minutes Following Intravenous Injection of 75 or 100 mg. Hydroxyzine

	No. of Patients	Control	Following Hydroxyzine
Cardiac output (L./min.)	5	6.0	6.4
Heart rate (beats/min.)	4	77	78
Mean arterial pressure (mm./Hg)	4	82	82

dosages employed. These effects persisted for one to four hours. The youngest patient to receive this drug complained of a disturbingly bitter taste in her mouth during injection. This patient had a large right to left intracardiac shunt.

Hemodynamic Studies: Pressure measurements in the radial artery, right ventricle and pulmonary artery were not significantly altered following injection of hydroxyzine. Cardiac output was slightly increased in two patients and slightly reduced in three patients, but the differences were not significant. The average values of cardiac output, heart rate and mean arterial pressure are shown in Table III.

COMMENTS

The present studies confirmed that hydroxyzine is an effective sedative. Effects on heart rate, arterial pressure or cardiac output were negligible. No deleterious side effects followed its intravenous use in large amounts in cardiac patients, indicating a relatively wide margin of safety.

Earlier reports suggested that hydroxyzine has a primary effect on the heart which makes it useful for the control of certain cardiac dysrhythmias.[1,2] The present trials on a similar series of patients have not demonstrated its effectiveness for the treatment of such rhythm abnormalities and hemodynamic studies have not indicated a significant cardiac action in terms of the conventional parameters that were measured.

The amounts of hydroxyzine that were used by the intravenous route were in most instances considerably higher than those employed by the oral or intramuscular route in the successful cases reported by Burrell et al.[2] Sedative action was marked. It is therefore unlikely that the absence of definitive responsiveness is the result of inadequate dosage.

Following completion of these studies, a report by Ziffer and Klotz[5] described the use of hydroxyzine in thirteen patients with cardiac dysrhythmias. The drug was administered by the oral, intramuscular, or intravenous route in somewhat smaller amounts. Beneficial effects were observed in two patients with supraventricular tachycardia. One patient who initially had a sinus rhythm manifested atrial fibrillation during the period of therapy. No effect was noted in ten of the patients. DiPalma[6] has found that the effectiveness of hydroxyzine is approximately equivalent to that of phenobarbital in ablating certain types of premature ventricular systoles. Expressing doubt that hydroxyzine is a drug which has a direct effect on the heart, DiPalma suggested that its activity and safety by the intravenous route deserves study. This has been accomplished in the present work. It was also apparent in the present experiments that this agent is primarily a sedative, when used intravenously, rather than a drug with antiarrhythmic potency. The very lack of cardiovascular action may actually prove to be of considerable clinical usefulness. In recent trials, hydroxyzine injected intravenously has been effective and safe during emergencies which required rapid sedation of patients with heart disease. It has been particularly helpful in controlling anxiety during cardiac catheterization and other physiologic studies.

SUMMARY AND CONCLUSIONS

Clinical and electrocardiographic studies in twelve patients with cardiac dysrhythmias were made to assess the therapeutic value of hydroxyzine. No definite antiarrhythmia action was demonstrated. Five subjects who had normal cardiac rhythm had no change in electrocardiogram, heart rate, arterial pressure or cardiac output following its intravenous injection. There was no evidence that hydroxyzine is an antiarrhythmic agent or that it has a primary cardiovascular action in human patients. However, intravenous administration of the drug appears to be safe and effective for rapid sedation of cardiac patients.

REFERENCES

1. HUTCHEON, D. E., SCRIABINE, A. and MORRIS, D. L. Cardiovascular Action of hydroxyzine (Atarax). *J. Pharmacol. & Exper. Therap.*, 118: 451, 1956.

2. Burrell, Z. L., Gittinger, W. C. and Martinez, A. Treatment of cardiac arrhythmias with hydroxyzine. *Am. J. Cardiol.*, 1: 624, 1958.
3. Nicholson, J. W., III and Wood, E. H. Estimation of cardiac output and Evans blue space in man, using an oximeter. *J. Lab. & Clin. Med.*, 38: 588, 1951.
4. Weil, M. H. and Sudrann, R. B. Use of simplified oximeter amplifier for measurement of oxygen saturation and dye concentration during cardiac catheterization. *Circulation*, 20: 782, 1959.
5. Ziffer, A. M. and Klotz, S. D. The use of hydroxyzine in the prophylaxis and therapy of cardiac arrhythmias. *Am. J. Cardiol.*, 5: 413, 1960.
6. DiPalma, J. R. Pharmacology of drugs used in cardiac arrhythmias and disturbances in conduction. *Prog. Cardio. Dis.*, 2: 343, 1960.

Historical Milestones

An Encyclopedic Treatise on Embolism

(Bernhard Cohn, 1860)

SAUL JARCHO, M.D.

New York, New York

AMONG the pleasures and obligations of historical writing not the least important is the resurrection of forgotten treasures of the past. Cardiology is especially rich in its heritage, much of which deserves to be rescued from oblivion.

In his classic essay on embolism,[1] William Welch made the following statement:

"Cohn's remarkable book,[2] published in 1860, is extraordinarily rich in anatomical, experimental, and clinical facts, and it is well for anyone who believes that he has a new observation or opinion concerning embolism to consult it before venturing on publication; a precaution which has evidently been often neglected by writers on the subject."

The truthfulness and value of Welch's encomium are apparent in the following excerpts.

* * * *

EXCERPTS FROM BERNHARD COHN'S BOOK ON EMBOLISM

Phlebitis of the sinuses from caries of the frontal bone: Case 31. Carl Bischoff, shoemaker, age 27.... Caries of the frontal bone. Meningoencephalitis. Abscess of brain. Phlebitis of sinuses. *Anamnesis:* Patient previously had syphilis; severe frontal headaches for one year. Over the right frontal bone, redness of the skin and tumor gradually developed, which subsequently softened and was incised. Since then the wound has discharged extremely foul secretion. *Status praesens:* Carious area about 1 in. long and 3 in. broad on the right frontal bone. No headache, no disturbance of consciousness. Digestion nearly normal. No fever. *Course:* On July 27 the first epileptoid attack, preceded by irritative phenomena especially on the left side. On July 30 a second attack, with fever in the evening. Similar attacks until August 5; the tongue mobile, the left upper extremity paretic. In general great apathy, inclination to coma, diarrhoea.... In the last two days complete unconsciousness, no further convulsions. *Autopsy.* Over the right frontal and parietal bone there was loss of substance of the skin 2 in. long and 10 in. broad ... underlying bone was carious. Subjacent dura covered with purulent exudate; in the longitudinal sinus a firmly coagulated old clot, the wall infiltrated with pus. Corresponding to the site of the wound the cerebral cortex was softened and dirty gray, the adjacent region swollen. Beyond this a second focus of softening, as large as a walnut, which had broken into the ventricle.... Scar of chancre on penis to right of frenulum.

Aside from headache, which in all probability was caused by the disease of bone and meninges rather than by the thrombosis, there was no symptom that could be referred to the latter. This case offers more of interest with respect to etiology than diagnosis. The thrombosis was obviously older than the involvement of the brain in the general process and had preceded it by a long time. I might put it in the category of the so-called haemorrhagic thromboses of Dusch. The veins of the diploe of the frontal bone could have produced it by simple direct continuity. If the thrombosis had originated in the cerebral inflammation, the pia in the vicinity would have been more severely affected than was actually the case and the coagula would have become purulent. The walls of the sinus had begun to participate in the general inflammatory process, but the thrombus itself had no purulent characteristics and must have been formed a long time previously ....

Thrombosis of the uterine veins: Case 34. Thusnelda Jackisch, servant maid, age 29.... Metrophlebitis

extending to the left spermatic vein. Pyaemia. Intermuscular abscess of the leg. *Anamnesis:* Parturition 11 days previously; two days thereafter the first chill; entirely normal after this until 2 days ago. Discharged from the clinic. Pains in both lower extremities, especially the left; shivering, anorexia, insomnia, thirst, swelling of left foot. *Status praesens:* High fever. Pulse 112. Dry tongue. Lack of appetite. Slight cough. Large spleen. No lochia. Uterine region not tender. Left calf swollen, slightly red. Thin pale yellow stool. Albuminuria. *Course:* Persistence of thin stool and albuminuria, no chills, no cough. Pulse 104–116. Sensorium clear. On July 13 a half-hour's chill; the same occurred twice on the next day, with increased force. Vigorous cough from then on; sputum unremarkable. No jaundice. Marked loss of strength. Death with customary phenomena of pyaemia. *Autopsy:* . . . In the small pelvis a little free pus. Both kidneys strongly and recently infiltrated, swollen. From the left surface of the uterus the readily palpable internal spermatic vein extends to the vena cava; it is filled with firm coagula and with putrid and diphtheritic fluid. In the uterus it is composed of a large number of small suppuratively inflamed and in part abscess-like phlebitic configurations and constitutes the immediate continuation of these. The internal wall of the uterus is covered with dirty layers, especially on the left side, corresponding to the former site of placental attachment. Left ovary and tube somewhat injected. Femoral veins clear. In the left gastrocnemius foul destruction reaching to the heel. In the corresponding place on the right side an abscess as big as a pigeon's egg, with benign content.

The relation of the phenomena given here was easy to recognize. I have considered this case especially worthy of report because it gives us a simple picture of the condition which we so often see developing in the puerperium under many designations and complications, and which has often been given the vague generic name of puerperal fever. From the genuine simple metrophlebitis which had engendered itself anew because the veins at the placental site had become inflamed because of defective uterine contraction and supplied a purulent and self-decomposing secretion, the process extended next to the spermatic vein, which showed such tense and thick walls that one might mistake it for a branch of the iliac vein. From here was introduced a purulent infection of septic type, which, since firm large particles were not flushed forth, produced no lung abscesses but was well suited to produce, on the arterial side, the abscess in the leg.

The diagnosis in this case was very difficult. Specifically, confusion with a typhoidal process was easily possible. The decision was given solely by the development of chills, which occurred late. . . . Moreover, in the puerperium a typhoidal disease of the blood is uncommon; much that has been taken to be such, has revealed itself by unprejudiced test to be pyaemia.

The region of the uterus, the portio vaginalis and vaginal mucosa were not tender. This fact, so impressive in itself and so noteworthy diagnostically is explained only by the patient's stupor, which resulted from general depression of cerebral function. The temperature, however, was greatly elevated. . . . That there was no edema of the vulva is due simply to the fact that only the internal pudendal vein was obstructed; the external pudendal, which empties into the iliac, had a completely unobstructed flow. . . .

The following very unusual case is of great interest. It exemplifies the puerperal process accompanied by . . . extremely noteworthy complications.

Case 36. Robertine Wenzlow, dressmaker, age 27, March 21 to April 22, 1859. Puerpera. *Thrombosis of the vena cava from the femoral vein to the hepatic vein:* Embolism of pulmonary artery. Gangrenous infarct of lung. *Anamnesis:* Always healthy. Until childbirth she worked strenuously as dressmaker. . . . Entirely healthy during this pregnancy. No edema of the feet, no vomiting, good appetite until almost the end. After very strong labor pains she was delivered of a healthy living child in one hour. Placenta was detached by the midwife; blood-loss very scanty. Lochia ceased entirely as early as the second day. The patient felt well . . . and continued to be vigorous until the ninth day. Then, while walking back and forth in her room, she had a violent chill followed by fever and sweating. The recurrence of this on the next day, the anorexia, and the general weakness of the extremities led to the request for medical aid. *Status praesens:* Woman of delicate constitution complaining mainly of severe headache, thirst, burning skin, vague abdominal pain, anorexia, diarrhoea. Uterine region not swollen. Internal examination reveals no elevation of temperature, no tenderness, small flow of lochia, not foul. Urine contains urates, no albumen. No cough, no dyspnoea. No edema of lower extremities. . . . *Course:* Lochia did not become more profuse. Chills returned daily or more often, at irregular times, and with variable intensity. Main complaint intense diffuse headache, somewhat alleviated by ice-cap. Occasional attacks of dyspnoea, nearly without cough; no expectoration. . . . Ten days later, sticking pains in right chest, especially on deep

inspiration; pleuritic rub audible. From now on, annoying cough; presently signs of pneumonia in right middle and lower lobes; expectoration dirty gray, partly bloody. Frequent hiccough. No albuminuria. Massive edema of both feet. Profuse sweats. General collapse; pulmonary edema. Chills up to the last day. Death on 31st day after parturition. *Autopsy:* . . . Right lower lobe compressed by acute purulent pleural effusion; both upper lobes edematous only. The pulmonary artery of the right middle and lower lobes shows multiple obstructed lumina; the thrombi are mostly purulent and white; the adjacent wall thickened, opaque; at many places there are knobby purulent prominences under the intima. The nearby parenchyma was becoming abscessed, often forming large cavities filled with malodorous pus; many foci were still in the stage of haemorrhagic infarction. . . . Heart small . . . endocardium clear. . . . Spleen small, pale, without infarcts. . . . Uterus in small pelvis, almost completely involuted; its internal lining still shows the placental site; here are lumina of many veins which are filled with firm non-purulent thrombi; uterine substance normal. Veins of pampiniform plexus greatly dilated, contain fluid blood. Ovaries intact. No purulent collection in pelvis; no caries. Vena cava palpable against the vertebral column as a hard cord, firmly adherent to the brownish-red injected wall, partly discolored, not completely filling the lumen. These strands go through the liver and above the diaphragm but do not extend backward to the ramifications of the hepatic veins. Almost all tributary collaterals, even the left renal vein, contain old thrombus. The process extends retrograde into both lower extremities, and ends on the left in mid-thigh; the vessels here bulge with thin blood. Collateral channels in this region are firmly thrombosed. Feet not edematous. Epigastric vein three times as wide as normal, not obstructed; superficial veins of the extremities empty also. . . . Azygos vein greatly dilated, contains freely movable blood.

The manner of formation of this very widespread thrombosis is not so easy to interpret exactly. . . . The simplest explanation would be to regard it as puerperal, i.e., as one of those associated in whatever way with involution of the uterus. This however is highly improbable. The uterus was entirely normal; its cavity was of the usual dimensions; its internal wall was markedly reddened and showed merely a few irregular areas of roughness at the site of placental attachment. There was no diphtheritic exudate. The uterine veins for the most part were empty, but a few of them were filled with firm, white coagula which had not become purulent. There was no continuous thrombosis extending into the pampiniform plexus, or into the hypogastric vein. . . .

The lochia had ceased early, yet the patient had had no complaints and had manifested neither pain nor febrile irritation of the vascular system. Moreover the vaginal temperature was not elevated and the portio vaginalis was not tender. Thus the assumption that the lack of lochial discharge is related to diseases of the uterus must be rejected as untenable, like the further inference that suppression of the so-called critical secretion causes such thromboses and chills. The notion of the critical importance of lochial discharges is to be applied only between narrow limits. Such discharges should be regarded almost exclusively as the local secretion of a wounded and ulcerated mucosal surface which is on the way to healing.

Even if suppression of the lochia is frequently accompanied by further damage to the organism, the relation of these two occurrences must not be regarded as reciprocally conditioned. While the patient has fever, the lochial discharge, like many other physiological processes, is impaired; the converse is not true. Often enough the relation is coordinate. A traumatic or rheumatic metritis, for example, can produce fever and suppression of lochia simultaneously. The notion of the lochia as inherently a *materia peccans*, the resorption of which is conducive to thrombosis and other febrile puerperal processes, does not correspond with the best modern views. When the uterine cavity does not involute, when secretion stagnates and decomposes, when a membranous inflammation establishes itself on the mucosa, then an intoxication can of course be conveyed to the blood, and can accomplish this because it leads to phlebitis with the formation of corrupted purulent disintegrating thrombi. In our case we can see in the early cessation of the discharges nothing more than a puerperal involution that had run an especially favorable course. The delivery occurred easily, the placenta was well separated, lactation had developed normally. For the first ten days the patient remained entirely well. Then a chill suddenly occurred. Hence thrombosis must have been present already, under conditions that made embolization possible. Apparently spontaneous thromboses are known to occur in the puerperium in the remote parts of the venous system, but these usually have their special basis in severe prolonged marasmus; such was not the case here. In the present case,

on the contrary, the length of the illness, and the patient's resistance to her frequent chills, complete anorexia, and severe pulmonary disease, gave evidence of a very sound constitution.

Moreover, despite the enormous and virtually total obstruction of the vena cava, there was no edema of the feet and no ascites. This shows that the thrombosis had developed gradually and that there was opportunity for the development of adequate venous collaterals. The azygos vein and the epigastric veins were enormously dilated. This compels the assumption that the thrombosis had originated long before the childbirth. In my opinion it is unnecessary to think the disease was caused by compression of the vena cava resulting from pregnancy. In this small woman the abdomen was so large that twin pregnancy was suspected. To this factor another one, very noteworthy, was added, i.e., patient's occupation, which required constantly a bent posture of the upper part of the body. The thrombosis terminated exactly at the point where the veins go through the diaphragm, i.e., at the apex of the angle formed by the patient's bent posture. As long as the patient was pregnant, deleterious effects were not evident and her condition was normal. The delivery was rather quick and easy. Notably, excessive haemorrhages were not observed, although the openings of the hypogastric veins into the iliacs were entirely occluded. The numerous anastomoses between the uterine veins, between the pampiniform plexus and the haemorrhoidal and epigastric veins, between the spermatic veins and the azygos, etc., must have been completely sufficient to compensate for the aforementioned obstruction.

What was the source of the emboli in the puerperium? What caused the crumbling of the thrombi in the vena cava? Why did they later assume a septic character and cause lung abscesses? In my opinion the following additional facts must be considered. At the start of the puerperium, the pressure of the uterus on the vena cava was suddenly relieved and the lumen of the vein had to return to its previous size. Here we must formulate a hypothesis similar to that of Burrow in cases of amputation. . . . In the first few days the collateral channels afforded adequate run-off for the newly redirected blood currents and thus prevented excessive pressure and speed in them. Therefore in the first ten days almost nothing happened except crumbling of the coagula; the serous part of the flowing blood moistened the old firm thrombi. When the patient stood up, strong muscular movement was unavoidable. Consequently, according to well known physiological principles, general increase in venous pressure being assumed, the current in the vena cava attained enough strength not only to detach crumbled thrombi but also to carry them onward. Through the repetition of this occurrence the capacity of the lungs was appreciably reduced, and anorexia, anemia and persistent febrile irritation developed.

Thus the originally bland and simple fibrinous formations deteriorated into a chemically corrosive and different material. This produced sporadic local inflammation, manifested in abscess formation in the contiguous wall of the vessel; naturally it caused similar effects in the pulmonary artery also.

In this way the etiology and the pathologic-anatomic process in the present case appear to be completely explained. As to diagnosis, the chills, the atypical course, the complete ineffectiveness of large doses of quinine, and finally the emergence of metastatic pulmonary disease justified the suspicion of embolization. Detection of the sources was lacking. There was no symptom which pointed to a uterine origin. The vaginal temperature was not elevated; the portio vaginalis was not swollen or painful; the uterus was completely contracted; lochia was absent. Chills first appeared on the tenth day. Phlegmasia alba dolens and edema of the feet were absent.

Thrombosis of the vena cava produces no definite syndrome. Penetrating pains in the interior of the trunk, dryness of the tongue, and a sense of pulsation in the scrobiculus cordis have been alleged in this connection. Among others Reumert (*Dissertation on the symptoms of inflammation of the vena cava.* Copenhagen, 1840) has attempted to produce inflammation of the vena cava in animals and to study the symptoms. His results were entirely negative. Mine were as follows:

Experimental thrombosis of the vena cava: Experiment 1. In a very small dog on Aug. 15, 1858, a German silver sound was introduced into the left femoral vein and thrust forward up to the epigastric region. On awakening from the chloroform anesthesia the animal howled a little, limped to its resting-place, and was rather quiet. On Aug. 16 at 11 A.M the animal could walk well, but the left hind leg appeared somewhat swollen, especially in

its upper portion; appetite maintained; vomiting not observed; pulse 120, respir. 32; cardiac rhythm irregular; no fever; moderate apathy Aug. 17, 5 P.M. . . . no dyspnoea; edema of the left leg has increased; the wound is more intensely inflamed . . . high fever. Aug. 18: the dog lay huddled in a corner, very apathetic; marked shivering; no appetite. . . . Aug. 19: inability to stand, stertorous respiration, marked cardiac irregularity. . . . Died during the night.

Autopsy: The sound was far above the diaphragm. It was enveloped by masses of thrombus, which consisted mostly of simple crumbling fibrinous material, partly discolored, attached to the wall of the vein. The inner wall of this vessel was reddened at intervals; the right iliac vein was clear; the left was obstructed up to the point of ligation; both renal veins empty. Lungs engorged with blood, somewhat edematous; pulmonary artery free from coagula; heart valves normal; no free fluid in abdomen. . . . Both kidneys were anemic. No urine in bladder. Vicinity of the vena cava free from evidences of inflammation.

The sequelae were also very scanty. The absence of ascites, of edema of the lower extremities, and venous hyperemia of the kidneys is sufficiently explained by the fact that the obstruction of the vena cava was incomplete. The absence of embolization is more difficult to explain. The cause must be sought in two considerations. The lateral currents had found collateral pathways, through which they were directed away from the vena cava. Specifically, however, the induced trauma was so intense that the economy of the entire organism must suffer; hence with the phenomena of high fever, complete anorexia, in a short time general marasmus necessarily appeared. Finally the pulse was impalpable and cardiac action became very irregular. Thus the power of the heart became inadequate to drive the arterial blood to the periphery. Presumably its action in the venous system must have been even less.

* * * *

Author's Comments

The excerpts which have been given represent very clearly the condition of medicine between the major discoveries of Virchow and those of Pasteur. Virchow's great work on thrombosis and embolism had appeared in 1846; its influence is visible in almost every paragraph of Cohn's treatise, which is essentially a translation of the doctrine of thrombosis and embolism from the dissecting room to the bedside. The only important gap is that of bacteriology.

Cohn's work is additionally significant because it exemplifies the close relation between morbid anatomy and clinical diagnosis. In this respect it follows directly in the tradition of Auenbrugger, Corvisart and Laennec.

The thoroughness of the anatomic study in Cohn's cases is well worthy of our attention, especially since nowadays we are accustomed to witness a rapid and comparatively perfunctory dissection supplemented by detailed microscopic analysis.

It should also be noted that Cohn used the autopsy findings as a basis for an anatomic *and physiologic* reconstruction of morbid processes. He then sought additional clarification by recourse to experiment. The autopsy thus contributed to the explanation of the clinical course but also suggested problems for further investigation.

These facts have special relevance at the present time, inasmuch as the autopsy has recently been subjected to attack in the American medical literature. Fortunately, there has been no lack of capable and articulate defenders.

References

1. Welch, W. Embolism. In: Allbutt's System of Medicine, vol. 7, pp. 228–285. London, 1899. Macmillan Co.
2. Cohn, B. Klinik der embolischen Gefässkrankheiten, mit besonderer Rücksicht auf die ärztliche Praxis, Berlin, 1860. Hirschwald. The excerpts given herein are from pp. 195–6, 201–2, 204–9 and 209–10.

Case Report

Ruptured Sinus of Valsalva Aneurysm

Clinical Features*

R. E. Rossall, M.D. *and* R. S. Fraser, M.D.

Alberta, Canada

A number of instances of ruptured aneurysm of the sinuses of Valsalva have been recorded in recent years. Morgan-Jones and Langley[1] have reviewed the published cases up to 1949. Oram and East[2] in a scholarly account have added two further examples in one of which the diagnosis was made during life. Most recent reports[3–5] have laid particular emphasis upon surgical repair of these defects.

Correct diagnosis, while depending primarily on awareness of the syndrome produced by rupture of such an aneurysm, has rested largely upon the clinical findings and upon radiologic studies of varying complexity. While such studies have on occasion produced diagnostic evidence of the lesion,[3,6] they have on at least two occasions led directly or indirectly to the death of the patient.[7,8] Little aid has been obtained from the electrocardiogram and the statement by Oram and East[2] that "E.C.G. findings are so inconstant that they give little assistance to diagnosis" appears to be the consensus.

We would like to add two further instances of ruptured congenital aneurysm of a sinus of Valsalva; the findings from these patients provide interesting contrast with each other. One was successfully treated surgically; the other died on the day scheduled for operation.

Case Reports

Case. This patient, a thirty-four year old housewife, was admitted to the hospital in congestive heart failure in June 1958. She gave a history of a heart murmur having been recognized at the age of ten years. She had been seen elsewhere in January 1957, during her second pregnancy, at which time she was symptom free and her heart size was normal. However, on examination she had a systolic thrill and murmur at the base of the heart in the second and third left intercostal spaces and a soft decrescendo murmur in the fourth left interspace. Her blood pressure was 130/70. She continued through her pregnancy uneventfully.

Late in February 1958, she noted the sudden onset of a dry cough and acute shortness of breath on exertion. Ankle edema followed and she remained in congestive heart failure with only transient improvement until her admission to the hospital.

Physical Findings: On examination the jugular venous pressure was elevated to 8 cm. above the sternal angle. A dominant "V" wave was present in the jugular venous pulse. The radial pulse rate was 120 per minute and the pulse was collapsing in quality. The brachial blood pressure was 150/45 mm. Hg. The apex beat was formed by a hypertrophied left ventricle and was in the sixth left interspace in the anterior axillary line. There was a pronounced heaving impulse over both the right ventricle and the right ventricular outflow tract. Both systolic and diastolic thrills were present along the left sternal border. On auscultation at the apex the first sound was diminished in intensity. A transmitted late systolic murmur was heard and a short, rumbling, mid-diastolic murmur was also present. At the base of the heart the second sound was split, the duration of splitting varying with respiration. The pulmonary element was moderately accentuated. An ejection systolic murmur, grade 3 in intensity,† was present along the left sternal border and a long decrescendo murmur, grade 4 in intensity, was heard in the same position following the second heart sound. Both murmurs radiated widely to the left of the

† Murmurs are graded 1 to 4 in intensity.

* From The Department of Medicine, University of Alberta and Cardiopulmonary Unit, University Hospital, Edmonton, Alberta, Canada.

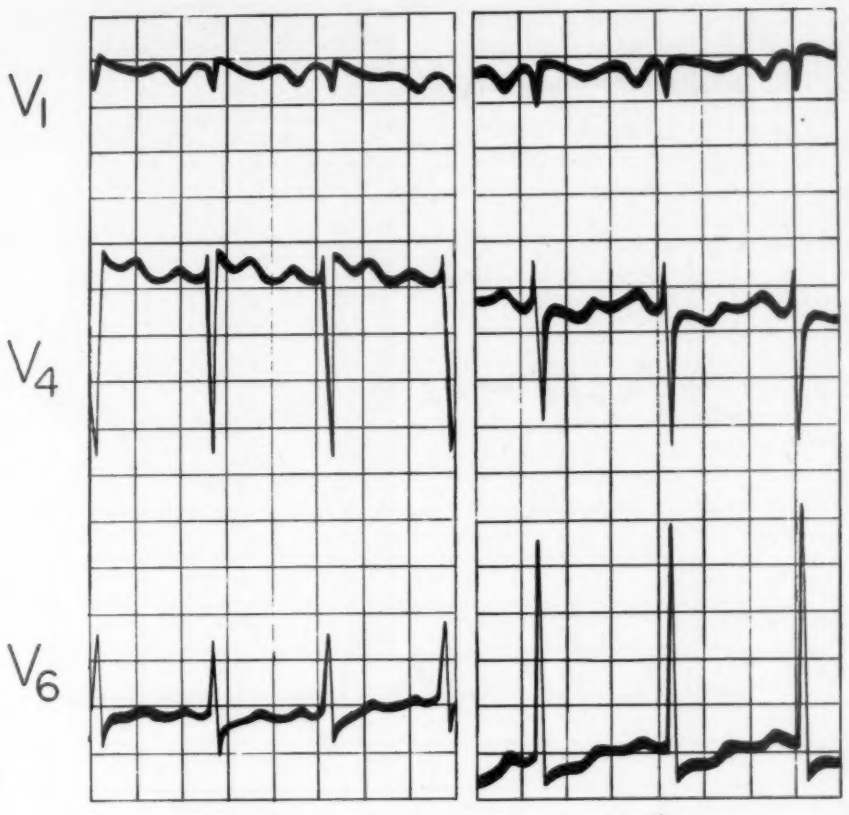


FIG. 1. Case 1. Electrocardiograms; precordial leads V_1,V_4,V_6. A, June 9, 1958; B, July 10, 1958. Time lines = 0.20 second.

sternum over the upper precordium. The liver was enlarged two fingerbreadths below the right costal margin. Slight edema of the ankles and feet was present. Air entry was normal on both sides of the chest and no adventitious sounds were heard.

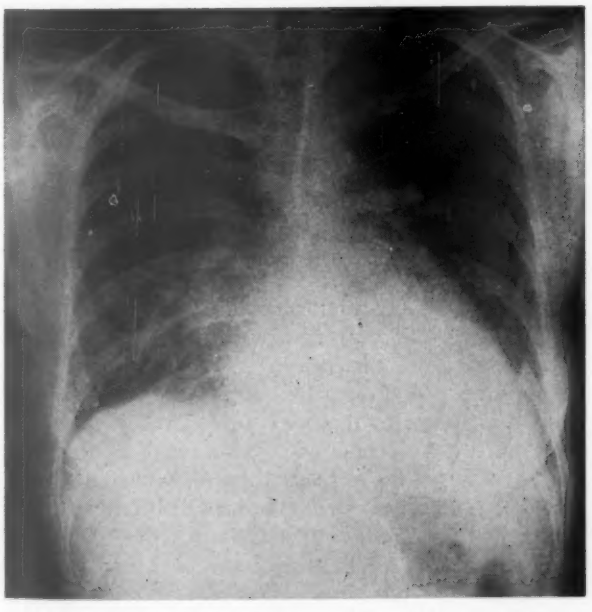


FIG. 2. Case 1. Posteroanterior roentgenogram.

Electrocardiograms taken in June and July 1958—one month apart—showed rapidly developing left ventricular hypertrophy and strain (Fig. 1). The chest radiograph taken in June (Fig. 2) showed an enlarged heart and evidence of pulmonary congestion.

TABLE I
Catheterization Data in Case 1

Position	Oxygen Saturation (%)			Pressure (mm. Hg)
	Oximeter		Van Slyke	
	1*	2*		
S.V.C.	63	52	59	—
R.A.	54	43	—	(8)
R.V. (mid)	—	42	—	49/11 (27)
R.V. (outflow)	62	58	—	—
P.A.	68	62	68	46/21 (34)
Femoral	—	—	97	—
Cardiac output (Systemic flow)			3.1 L./min.	
Pulmonary Flow			4.1 L./min.	

* 1 and 2 represent separate series of O_2 saturation determinations taken in rapid sequence.

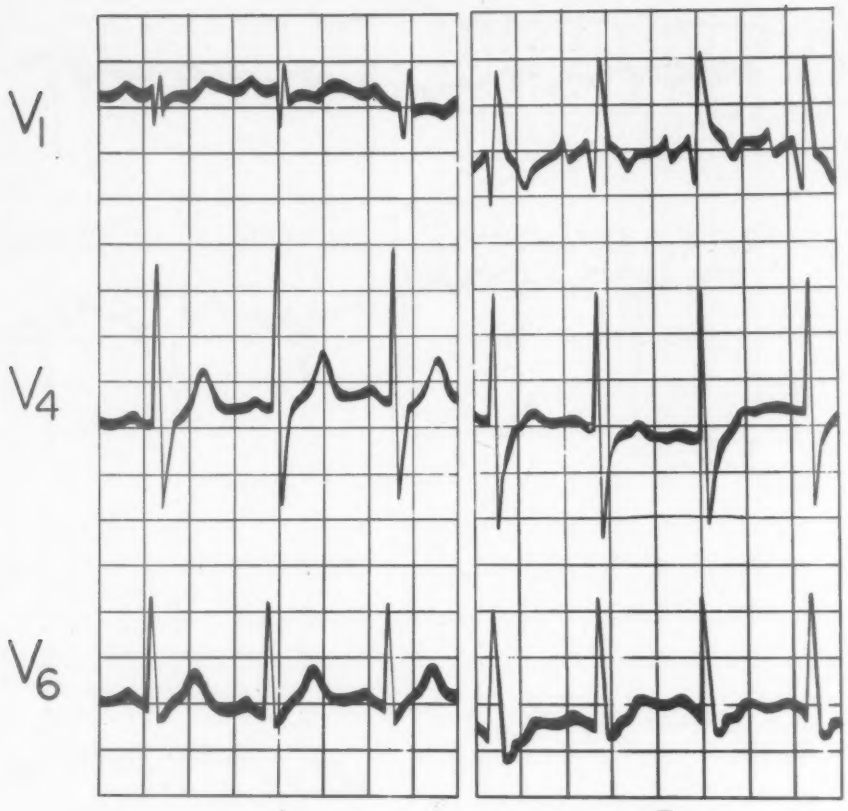


FIG. 3. Case 2. Electrocardiograms; precordial leads V_1,V_4,V_6. A, August 8, 1959; B, August 10, 1959. Time lines = 0.20 second.

Cardiac catheterization was performed during the admission in June 1958 and the results are given in Table I.

A presumptive diagnosis was made of interventricular septal defect plus sudden aortic insufficiency from rupture or prolapse of an aortic cusp, or rupture of a congenital aneurysm of a sinus of Valsalva into the right ventricle. The patient was discharged to await operation and was readmitted on July 8, 1958. The clinical findings were unchanged but the electrocardiogram showed increasing left ventricular hypertrophy and strain.

Operation was carried out using cardiopulmonary bypass on July 17, 1959. A ruptured aneurysm of the right sinus of Valsalva was found entering the right ventricle. The aneurysm was successfully excised and oversewn. The postoperative course was uneventful and the patient has remained well since.

Case 2. This patient, a fifty-six year old woman, was first admitted to the hospital on July 29, 1959, for operation on a hammer toe. On this admission a cardiac murmur was recorded, mainly systolic in time but beginning just before the first heart sound. This murmur was harsh and was maximal in the left fourth interspace adjacent to the sternum; it was accompanied by a thrill. The second heart sound at the base of the heart was normal. The blood pressure was 150/100. A chest radiograph revealed slight generalized enlargement of the heart. The patient appeared to be in good health and underwent the operation upon her toe with no difficulty. Following this she was discharged from the hospital.

On August 7 at noon, she experienced sudden onset of rapid palpitation, weakness and slight pain between the shoulder blades. The palpitation lasted some six hours and then gradually subsided. She was readmitted to the hospital on August 8, twenty-four hours after the onset of her symptoms.

Physical Findings: She was seen by one of us on August 10 at which time she was stuporous. Her extremities were cold, pale and clammy. The peripheral pulses (radial, posterior tibial) were not obtainable but the more proximal pulses (brachial, femoral) were present and were grossly collapsing in quality. The brachial blood pressure was 120/0. Vigorous carotid pulsations were evident but there was no venous distention. The apex beat was diffuse and poorly localized between the midclavicular and anterior axillary lines in the sixth left interspace. A pronounced heaving impulse was felt to the left of the sternum internal to the apex beat. Along both sternal borders a diastolic thrill was palpable. On auscultation at the apex the first sound was normal and a transmitted systolic murmur could be heard. At the base the second heart sound was single. A grade 2 systolic murmur was present,

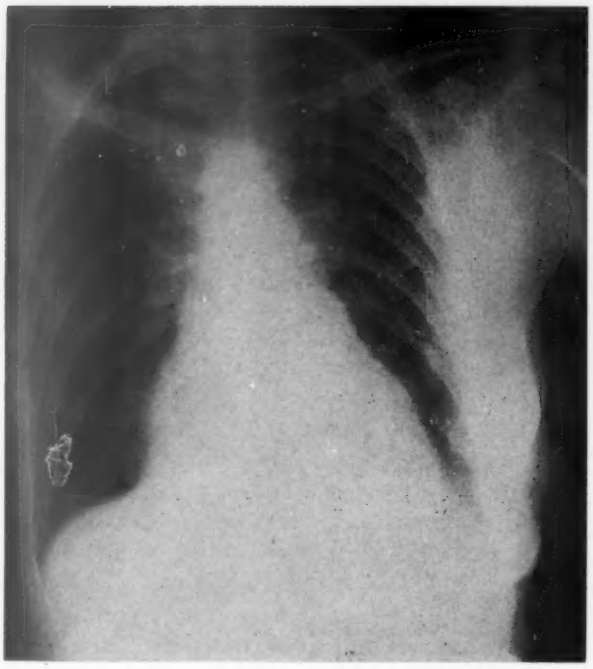


FIG. 4. Case 2. Posteroanterior roentgenogram.

radiating to the neck, and a grade 4 decrescendo diastolic murmur was heard radiating downward along both right and left sternal borders to the xiphoid. The liver was enlarged two fingerbreadths and was tender.

She remained semiconscious but after twenty-four hours the limbs became pink and warm; obviously collapsing pulses appeared at the wrists and feet and the jugular venous pressure became elevated. Prominent, late V waves became evident in the jugular venous pulse. Examination of the chest revealed good air entry and no adventitious sounds.

Electrocardiograms taken on August 8 and August 10, 1959 (Fig. 3) demonstrated rapidly increasing right ventricular strain with delayed conduction. *Chest radiography* revealed a rapid increase in heart size (Fig. 4).

A diagnosis of rupture of an aneurysm of a sinus of Valsalva into the right side of the heart was made and arrangements were initiated for operation using cardiopulmonary bypass. Her condition deteriorated rapidly, however, and she died early on August 12, the day scheduled for operation. *Autopsy* revealed a ruptured aneurysm of the right sinus of Valsalva into the right atrium.

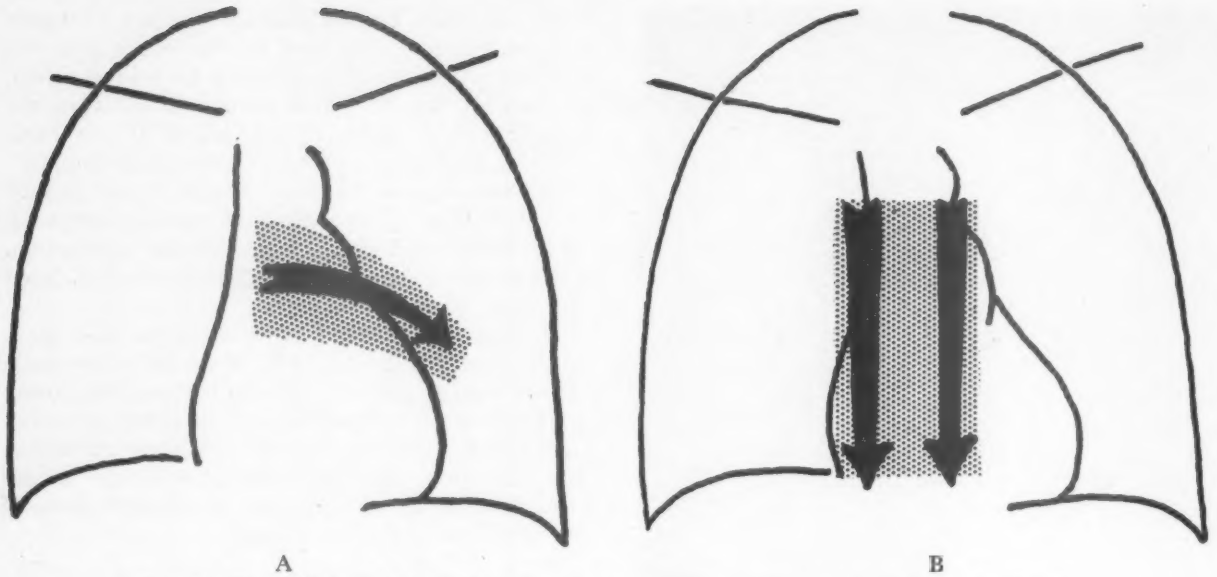
COMMENTS

In these two patients, one aneurysm ruptured into the right ventricle and one into the right atrium. The development of the physical signs and the electrocardiographic findings provide an interesting contrast (Table II).

Both patients presented with the sequence of events so well outlined by Oram and East,[2] namely, the sudden onset of symptoms, the appearance of either a "to-and-fro" or a "continuous" murmur, together with signs of periph-

TABLE II
Clinical Findings

Time	Case 1	Case 2
Prior to rupture	Systolic thrill and murmur in left 2nd and 3rd intercostal spaces Early diastolic murmur along left sternal border	Presystolic and systolic murmur in left 4th intercostal space
After rupture (peripheral)	Jugular venous pressure: raised Jugular venous pulse: moderate V wave Arterial pulse: collapsing Blood pressure: 150/45 mm. Hg	Jugular venous pressure: became raised Jugular venous pulse: prominent late V wave Arterial pulse: collapsing Blood pressure: 120/0 mm. Hg
After rupture (precordium)	Apex: 1st heart sound diminished; short rumbling mid-diastolic murmur Base: 2nd heart sound split; grade 3 systolic murmur; grade 4 diastolic murmur and thrill Transmission of murmurs (see Fig. 5A)	1st heart sound normal; no diastolic murmur 2nd heart sound single (pulmonary); grade 2 systolic murmur; grade 4 diastolic murmur and thrill Transmission of murmurs (see Fig. 5B)
Radiographic findings after rupture	Increasing heart size; plethoric lung fields; pulmonary venous congestion	Increasing heart size; plethoric lung fields; no venous congestion
Electrocardiographic findings	Developing left ventricular hypertrophy and strain	Developing right ventricular strain and delayed conduction
Chamber into which rupture occurred	Right ventricle	Right atrium



A B

FIG. 5. Transmission of diastolic murmur after rupture occurred. A, Case 1; B, Case 2.

eral diastolic collapse and intractable heart failure.

Cardiac Murmurs: Evidence of a cardiac lesion was present before rupture in each of our patients. Steinberg and Finby[9] in their description of the physical signs in nine patients with unruptured aortic sinus aneurysms state: "Common to all was a loud, rough (grade 2 to 4) systolic murmur at the apex of the heart, heard all over the precordium and especially to the left of the sternum. In three instances aortic valvular lesions were also present and produced diastolic and systolic murmurs at the base of the heart." Findings similar to these were recorded in Case 1 although the presence or absence of an aortic valvular lesion must remain undecided. The diastolic murmur, much more obvious after rupture of the aneurysm, disappeared after excision of the aneurysm from the right ventricle. This suggested to us that no aortic valvular lesion was present.

At operation in Case 1 a small opening, 1 mm. in diameter with well organized, rounded edges was found in the wall of the aneurysm. It lay quite separately from the extensive tear, the edges of which were not organized. It seems likely that the diastolic murmur heard prior to rupture may have been due to blood passing through the small hole from aortic sinus to right ventricle.

The murmur noted before rupture in Case 2 was mainly systolic although it began before the first heard sound. The reason for this is not clear but there appear to be two possible explanations. The aneurysm in this case arose from the right aortic sinus and was intimately related to the interatrial septum through which it ultimately ruptured. Atrial contraction may have produced distortion of the mouth of the sinus, thus creating turbulence in the aortic blood stream. The position and lack of radiation of the murmur fail to support the explanation. Alternatively, a small communication between aorta and right atrium may have been present before final extensive rupture occurred. Distortion of the atrial opening of the small fistula may have permitted blood flow to begin only during atrial systole whereas continuation of flow would result from rising pressure in the aorta during ventricular systole.

Whatever the explanation, it is clear that cardiac murmurs, not typical of those found in the commoner forms of heart disease, were present in both our patients. In each instance, too, the murmur was accompanied by a thrill before rupture occurred.

Murmurs Following Rupture: Following rupture of the aneurysms the physical signs were dominated by evidence of peripheral diastolic collapse and by precordial diastolic murmurs and thrills. In the first patient, however, clinical evidence for both left and right ventricular hyperactivity was present whereas in the second, hyperactivity was right-sided only. The differing transmission of the diastolic murmurs was doubtless due to the different site of rupture.

Attention is drawn by Levine[10] to "right-sided" aortic murmurs, such as that heard in

our second patient. Such murmurs apparently can be present both before and after rupture. Whether such murmurs occur after rupture into the right atrium only or whether they occur after rupture into other chambers is not clear from Levine's account. In his description of the murmur in a patient whose aneurysm communicated with the right ventricle, Levine states that the murmur was heard widely over the precordium. Our findings in Case 2 correspond closely to this description.

Electrocardiographic and Radiographic Findings: Despite Oram and East's contention that the electrocardiographic findings are so inconsistent as to give little assistance to diagnosis, the evolution of the patterns seen in the two patients presented here were so dissimilar that we believe some significance must be attached to them. The altered hemodynamics in our two patients resembled those found in patent ductus arteriosus and atrial septal defect, respectively. The electrocardiographic patterns came rapidly to resemble those commonly associated with these lesions.

The radiographic findings in these two patients were of limited value. Cardiac enlargement was present and known to be of recent onset. The lung fields had the appearance of increased blood flow in each instance and, in addition, appearances suggestive of pulmonary venous congestion were present in the first patient. No studies were made using contrast media.

Catheterization Findings: The catheterization findings from the first patient are presented because they appeared to us to be at variance with the physical signs. The shunt was relatively small (one-third of systemic flow) and yet the heart was grossly overactive and there was marked peripheral diastolic collapse. As stated above, we do not believe that aortic insufficiency played any part in this because all signs of diastolic collapse disappeared after excision of the aneurysm from the right ventricle. The unexpected degree of diastolic collapse could be due to shunting into a distensible chamber (the right ventricle) in which the diastolic pressure was very low during early diastole. Despite the similarity of the clinical pictures, it is of interest that the shunt demonstrated in our first patient was far less than those described by Brofman[6] (2.51 × S.F.),* Morrow[3] (2.57 × S.F.), Feldman[7] (1.8 × S.F.), Lin[8] (1.75 × S.F.) and Oram[2] (2.7 × S.F.).

* S.F. = Systemic flow.

Summary

From our experience with two patients with ruptured sinus of Valsalva aneurysms, we believe that there are so many unusual features in this form of cardiac disease that the diagnosis can be suspected not only before rupture of the aneurysm but also the march of events after rupture will indicate the site of rupture. Our first patient was young and she compensated for the sudden alteration in hemodynamics long enough to allow for both elaborate studies and elective surgery which was successful. Our second patient was older and she deteriorated rapidly. Surgery was planned but could not be instituted until too late and there was no opportunity for other than simple investigative procedures. It seems to us that when presented with this latter situation, immediate operation is required and the site of rupture can be predicted with some certainty from clinical and electrocardiographic findings.

Acknowledgments

The authors wish to thank Drs. J. Morgan and J. F. Elliott for information concerning the clinical status of these patients before rupture of the aneurysms occurred. The successful operation on the first patient was performed by Dr. J. C. Callaghan.

References

1. Morgan-Jones, A. and Langley, F. A. Aortic sinus aneurysms. *Brit. Heart J.*, 11: 325, 1949.
2. Oram, S. and East, T. Rupture of aneurysm of aortic sinus (of Valsalva) into the right side of the heart. *Brit. Heart J.*, 17: 541, 1955.
3. Morrow, A. G., Baker, R. R., Hanson, H. E. and Mattingly, T. W. Successful surgical repair of ruptured aneurysm of the sinus of Valsalva. *Circulation*, 16: 533, 1957.
4. Lillehei, C. W., Stanley, P. and Varco, R. L. Surgical treatment of ruptured aneurysms of the sinus of Valsalva. *Ann. Surg.*, 146: 459, 1957.
5. Bigelow, W. G. and Barnes, W. T. Ruptured aneurysm of aortic sinus. *Ann. Surg.*, 150: 117, 1959.
6. Brofman, B. L. and Elder, J. C. Cardioaortic fistula. Temporary circulatory occlusion as an aid in diagnosis. *Circulation*, 16: 77, 1957.
7. Feldman, L., Friedlander, J., Dillon, R. and Wallyn, R. Aneurysm of right sinus of Valsalva with rupture into right atrium and into the right ventricle. *Am. Heart J.*, 51: 314, 1956.
8. Lin, T. K., Crockett, J. E. and Dimond, E. G. Ruptured congenital aneurysm of the sinus of Valsalva. *Am. Heart J.*, 51: 445, 1956.
9. Steinberg, I. and Finby, N. Clinical manifestations of the unperforated aortic sinus aneurysm. *Circulation*, 14: 115, 1956.
10. Levine, S. A. and Harvey, W. P. Clinical Auscultation of the Heart, p. 490. Philadelphia and London, 1959. W. B. Saunders Co.

Diagnostic Shelf

WPW Syndrome vs. A-V Dissociation

An Unusual Series of Electrocardiograms*

ISIDORE STEIN, M.D., F.A.C.C.

Brooklyn, New York

DESPITE the advances in the past years of our knowledge of electrophysiology, the biochemistry and electrolytic patterns of the circulatory system, we are often hard put to offer a definitive electrocardiographic diagnosis. This may prove even more difficult in the absence of historic evidence of organic heart disease. We recently observed a patient who presented extremely bizarre electrocardiographic tracings. Numerous conflicting interpretations have been offered by various viewers. This case is therefore presented for diagnosis and discussion of the various possibilities.

CASE HISTORY

C. B., a forty-five year old white, married man, underwent routine physical examination. For the first time an electrocardiogram was taken. He had never had any symptoms relating to the cardiovascular system. A paternal aunt had diabetes and one brother had coronary thrombosis.

On examination, the patient was obese. Blood pressure on two occasions was 140 to 150/100 mm. Hg. Subsequently it was recorded at 110/80 mm. Hg over a period of several months. Examination and roentgenographic studies of the heart showed no enlargement. The rhythm was regular and there was no evidence of decompensation.

Laboratory studies revealed urinalysis to be normal; hemoglobin was 15.6 gm. per cent; red blood count, 5,250,000 per cu. mm.; white blood count, 9,500 per cu. mm. with a normal differential. Blood glucose and urea nitrogen were normal.

ELECTROCARDIOGRAPHIC INTERPRETATIONS

Figure 1 shows a regular ventricular rhythm at a rate of 75 to 78 per minute. The QRS complexes are 0.18 second in duration and have a bizarre form. They are not preceded by normal P waves. The main deflection in leads V_1 through V_5 is a tall R wave. A W-shaped QRS is present in lead V_6. It might appear at first glance that we are dealing with a rhythm of ventricular origin. However, particularly in leads I and V_5, there is an initial slurring of the upstroke of R, suggestive of a delta wave, as seen in the Wolff-Parkinson-White syndrome. In the search for atrial waves one discovers in lead aVL (long strip at the bottom of Fig. 1) an inverted P wave as a notch in the downstroke of the inverted T waves. Hence, it appears that the same focus which activates the ventricle sends its excitation backward causing a delayed stimulation of the atria.

Figure 2 reveals a predominantly regular ventricular rhythm whose complexes are largely identical with those of Figure 1. In addition there are upright P waves indicating a slightly irregular sinus rhythm that competes with the ventricular rhythm. Some of the normal P waves are obviously conducted to the lower chambers as indicated by the fact that they are followed at a normal interval (varying from 0.12 to 0.17 second in the various leads) by ventricular complexes of normal appearance (the fifth beat in lead II, the first beat in lead III, and the first four beats in lead V_1). Other beats which follow an upright P wave in short

* From the Department of Cardiology, Jewish Hospital of Brooklyn and State College of Medicine, Downstate Medical Center, Brooklyn, New York.

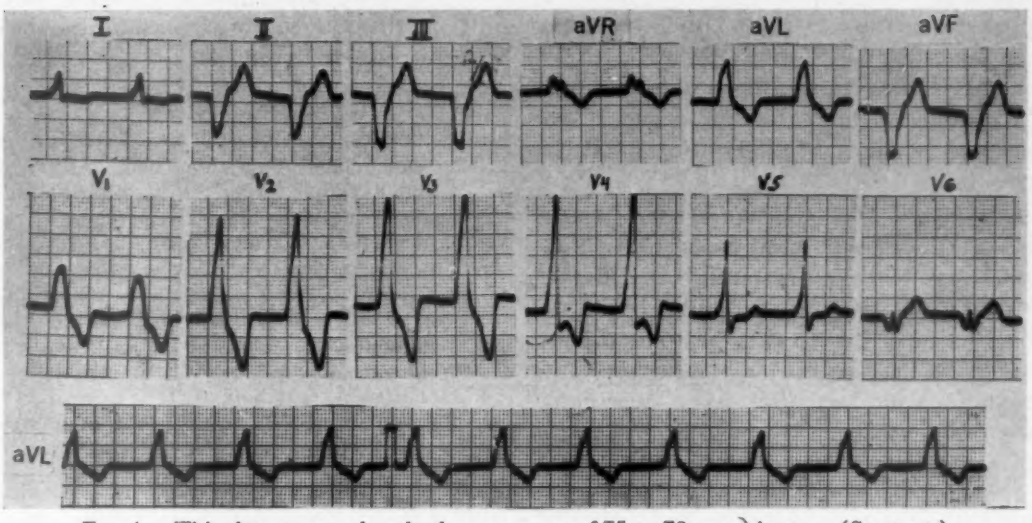


FIG. 1. This shows a regular rhythm at a rate of 75 to 78 per minute. (See text.)

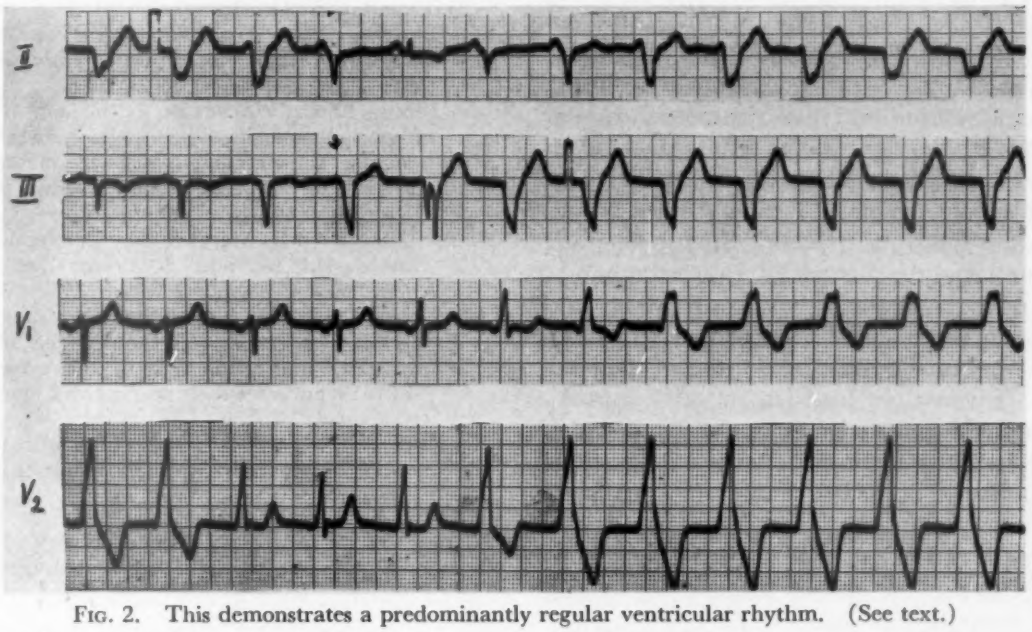


FIG. 2. This demonstrates a predominantly regular ventricular rhythm. (See text.)

intervals of varying lengths are clearly ventricular fusion beats (fourth, sixth through eighth beats in lead II, the fourth beat in lead III, the fifth to seventh beats in lead V_1, and probably the third to sixth beats in lead V_2).

Figure 3 demonstrates normal intraventricular conduction with a P-R interval varying between 0.16 to 0.20 second and QRS of 0.08 second. The T wave is inverted in leads II, III, aVF and V_6.

COMMENTS

There are several possibilities suggested by these tracings. The diagnosis of Wolff-Parkinson-White syndrome[1-5] is entertained by the

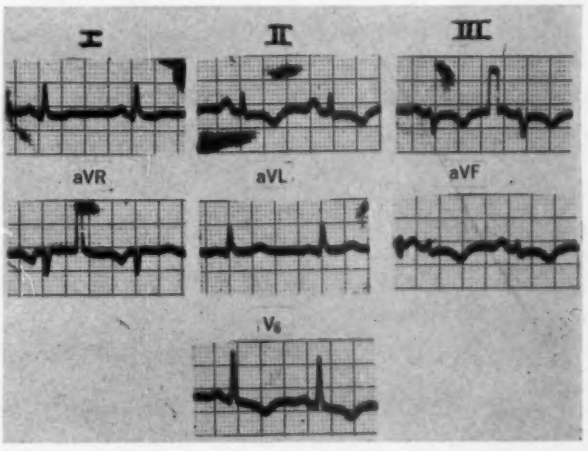


FIG. 3. This shows normal intraventricular conduction. (See text.)

presence of the delta waves and the widened, slurred or notched QRS interval. The presence of tall R waves as the main deflection in leads V_1 through V_5 lends further credence to the diagnosis of the Wolff-Parkinson-White syndrome.

Challenging this interpretation is the absence of a series of WPW beats with a constant short P-R interval. On the other hand, this tracing resembles the ones reported in the WPW syndrome by Pick and Katz,[6] first in isolated premature beats and later in the same patient in whom the ectopic focus has taken over control of the entire heart. We would then postulate in our patient that an abnormal focus is located in an accessory A-V bundle which competes with the sinus rhythm.

Another interpretation is that we are dealing with a basic A-V nodal rhythm and intraventricular block. The presence of ventricular fusion beats makes this diagnosis unlikely. One might assume that the bizarre ventricular complexes have a ventricular focus which sends waves of excitation backward to activate the atria whenever the latter have not been stimulated by normal sinus rhythm. Such retrograde stimulation by the ventricles is uncommon.[7]

Although this patient is asymptomatic and presents no physical or roentgenographic evidence of organic heart disease, the presence of inverted T waves in leads II, III, aVF and V_6 at a time when normal conduction is operative (Fig. 3) suggests ischemic changes in the diaphragmatic wall of the left ventricle. The nature of the disease, if any, can be elucidated only after prolonged study and observation.

References

1. Wolff, L., Parkinson, J. and White, P. D. Bundle branch block with short P-R interval in healthy young people prone to paroxysmal tachycardia. *Am. Heart J.*, 5: 685, 1930.
2. Wolferth, C. C. and Wood, F. C. Mechanisms of production of short P-R intervals and prolonged QRS complexes in patients with presumably undamaged hearts: hypothesis of an accessory pathway of auriculo-ventricular conduction (bundle of Kent). *Am. Heart J.*, 8: 297, 1933.
3. Holzman, M. and Scherf, D. Ueber Electrokardiogramme mit Verkuerzter Vorhof-Kammer-Distanz und Position P-Zacken. *Ztschr. klin. Med.*, 121: 404, 1932.
4. (*a*) Katz, L. N. and Pick, A. Clinical Electrocardiography. The Arrhythmias, p. 681. Philadelphia, 1956. Lea and Febiger.
   (*b*) Tamagna, I. G., Butterworth, J. S. and Poindexter, C. A. Wolff-Parkinson-White syndrome with myocardial infarction: an experimental study. *Am. Heart J.*, 35: 948, 1948.
   (*c*) Wood, F. C., Wolferth, C. C. and Geckeler, G. D. Histologic demonstration of accessory muscular connections between auricle and ventricle in a case of short P-R interval and prolonged QRS complex. *Am. Heart J.*, 25: 454, 1943.
5. Prinzmetal, M. Accelerated Conduction: The Wolff-Parkinson-White Syndrome and Related Conditions, p. 68. New York, 1952. Grune & Stratton.
6. Pick, A. and Katz, L. N. Disturbances of impulse formation and conduction in the pre-excitation (WPW) syndrome; their bearing on its mechanism. *Am. J. Med.*, 19: 759, 1955.
7. Barker, J. M. The Unipolar Electrocardiogram, p. 477. New York, 1952. Appleton-Century-Crofts, Inc.

Symposium on Monoamine Oxidase Inhibitors†

The Importance of the Monoamine Oxidase Inhibitors in Cardiovascular Disease*

GEORGE C. GRIFFITH, M.D., F.A.C.C.
Los Angeles, California

THIS SYMPOSIUM offers a unique opportunity to hear from outstanding authorities who have worked with the monoamine oxidase inhibitors in fields of basic biochemical mechanisms,[1] animal experimentation[2] and clinical evaluation in human subjects afflicted with cardiovascular pathology.[3–11]

The monoamine oxidase inhibitors offer a potent tool in the therapy of angina pectoris, a disease which has been very discouraging to treat either medically, surgically or by a combination of these methods. Two important facts are operative in angina: the psychic component and the factor of myocardial ischemia.

Iproniazid, the most widely used and the first of the monoamine oxidase inhibitors to come into general use, has proved very effective in the treatment of depressive states and in contributing to the patient's feeling of well-being. These benefits are of importance in the therapy of the patient with angina, who not only is limited in his capacity for effort but also is usually very fearful of the outcome of his illness. Several of the newer analogs of iproniazid are equally effective in relieving anginal pain but do not have the mood-lifting qualities of iproniazid or of one of its analogs, isocarboxazid.

The mechanism whereby the monoamine oxidase inhibitors accomplish their effects is not completely clear at this time. It is known that when preparations such as iproniazid are administered, a marked rise in serotonin and a moderate rise in norepinephrine result. Presumably, the increase is due to the inactivation of monoamine oxidase, which otherwise would destroy or by some other means remove from the circulation compounds such as serotonin, the catecholamines and their methoxy derivatives. We are not sure at this stage of our knowledge whether iproniazid's effects are dependent more on the increase in serotonin or on the increase in norepinephrine. In fact, it is entirely possible that products other than norepinephrine and serotonin are responsible for the observed effects: when normal pathways for metabolism are blocked by monoamine oxidase administration, other pathways may take over, and the accumulation of products normally present in small amounts may play a role in the central effects noted. Nevertheless, a temporal relationship can be demonstrated between the pharmacologic effects of preparations such as iproniazid and increase in the levels of brain serotonin and brain norepinephrine.

The most important benefit of the monoamine oxidase inhibitors, that which has been emphasized to me most forcefully in my own patients, and noted repeatedly by other investigators, is the ability of the patient previously disabled by angina to walk distances he was formerly unable to walk, and to go about his daily tasks, within

* From the Department of Medicine (Cardiology), School of Medicine, University of Southern California, Los Angeles, California.

† Presented at the University of Southern California School of Medicine, Los Angeles, California, March 3, 1960. General Chairman: George C. Griffith, M.D.

limits, without anginal pain or even feelings of pressure while receiving adequate dosages of these drugs. If the drug is stopped or reduced below the effective level for the individual patient, his capacity for effort again becomes increasingly limited, and he is forced to return to his pretreatment inactivity. Now, the foremost question is whether—with pain no longer a limiting factor on physical exertion of patients who respond well to the monoamine oxidase inhibitors—the patients may attempt too much for the pathologic state of the heart. Although I encourage my patients to resume activity commensurate with their physical limitations, I counsel them to increase activity gradually, allowing time for reconditioning of little-used muscles.

Clinical Experiences

Iproniazid: My first-hand experience with iproniazid (Marsilid®) has been limited, as I have administered the preparation to only fourteen patients, one of whom died of myocardial infarction within a few days of the start of medication, before the drug had received a sufficient trial. In two patients severe hypotension developed, which necessitated discontinuance of the drug in the first patient after only four weeks of therapy; the second died of uremia after seven weeks, during which time iproniazid afforded him no relief. One of the remaining eleven refused to continue treatment after the second week because he perceived no benefit. The ten patients who experienced benefit from iproniazid received between 50 and 150 mg. of the preparation daily for periods of four to thirty-two weeks, without significant complication except for slight euphoria in one patient. Angina stopped completely in these patients seven to fourteen days after the institution of iproniazid.

The cardinal drawback of iproniazid therapy, both in my experience and in other reports in the literature, has been the occurrence of orthostatic hypotension in a significant proportion of patients. Peripheral neuritis, too, has been reported in up to 20 per cent of patients maintained with iproniazid over long periods. The concurrent administration of pyridoxine (B_6) will eliminate or prevent the neuritis.

Perhaps the most dangerous complication of iproniazid therapy is the occasional occurrence of hepatotoxicity, possibly due to drug idiosyncrasy or to anoxia. This complication poses relatively little danger for the patient, provided frequent tests are made to determine the onset of hepatocellular abnormality. Screening tests for iproniazid hepatotoxicity should include at least a measure of serum transaminase (either SGOT or SLDH) and serum bilirubin. Serum transaminase studies provide earlier evidence of hepatocellular abnormality than flocculation tests do. Neither peripheral neuritis nor hepatic damage was noted in my patients.

Isocarboxazid: To overcome the deficiencies of iproniazid and other early monoamine oxidase inhibitors, several analogs of these preparations have been developed. The exact mechanism whereby these agents relieve anoxia is not understood completely, although *in vitro* studies and animal experiments with one of the newer iproniazid analogs, isocarboxazid (Marplan®), indicate that this product, too, potentiates the activity of biologic amines such as serotonin.

Thirty-one patients, twenty-one men and ten women, were treated with isocarboxazid for periods ranging from one to nine months. The patients studied ranged in age from their early forties into their seventies. All had angina pectoris; in some, the angina apparently was due to uncomplicated coronary atherosclerosis; in others, pre-existing myocardial infarction, hypertensive cardiovascular disease, aortic stenosis or heart failure was also present. About one-half were seriously ill. In this preliminary investigation, the patients were used as their own controls. I believe that this is acceptable in a pilot study such as this, as most of the patients had been under care for periods sufficiently long for me to know each patient's usual response to changes in procedure and medication. A response to the medication was judged by (1) severity of pain, (2) average number of daily anginal attacks, and (3) number of nitroglycerin tablets used.

Patients treated with isocarboxazid were started with small doses of the drug, usually 15 to 30 mg. daily in divided doses. At the outset 15 mg. per day was administered, and as the patients demonstrated tolerance, the dosage was increased. I rarely have administered above 30 mg. of isocarboxazid per day: the majority of my patients have achieved maximum benefit with medication in this range; several have been unable to tolerate more than 15 mg. per day. One patient, who first responded with nausea and vomiting to increases in dosage, was able to tolerate 20 mg. of isocarboxazid per day after the dosage was gradually increased by increments of 5 mg. daily at monthly intervals.

Catron: A second preparation, beta-phenylisopropyl hydrazine, has been administered to twenty-three patients with electrocardiographic

evidence of atherosclerotic heart disease. My customary procedure is to provide these patients initially with 9 mg. of the preparation per day, in divided doses. In patients who receive complete relief of their pain with this dosage, dosage later is reduced to 3 mg. twice daily.

General Effects of Therapy

In general, I have found that my patients have felt better under medication with iproniazid and its analogs than prior to the administration of these products. They are more alert, more cheerful, and they can do more than was possible formerly. Over 70 per cent of my patients report appreciable benefit from these preparations and, provided they are carefully observed for suggestions of any untoward effects and any tendencies thereto are corrected immediately, side effects are exceedingly rare. Usually, tension and depression give way to a state of relative tranquility. The next stage in therapy is the occurrence of a feeling of well-being, a reawakening of energy and a reaching out for new interests. This is the point at which I like to stabilize dosage, for with increased dosage, elation, overactivity and insomnia may appear, and the patient may become uncooperative and somewhat arrogant.

Side Effects: If the patient's knee jerks become excessively active, this should be interpreted as a sign that dosage should be reduced in order to prevent hyperkinesis. Whereas some patients will develop ravenous appetites and tend to gain weight, others will report anorexia with weight loss. These should be treated as soon as they make their appearance. Edema of the ankles in an occasional patient can be cleared with diuretics (I prefer not to use chlorothiazide, as it is potentiated by the monoamine oxidase inhibitors, rather, I use the organomercurials). An occasional patient may manifest subjective and objective evidence of discomfort, apprehension or an ill-defined sense of impending disaster. Ordinarily, this will subside spontaneously; in other instances, another monoamine oxidase inhibitor may be substituted for the one first given with better results. In the elderly, especially, a sharp drop in systolic and diastolic blood pressure may result in decreased cardiac output with congestive failure and peripheral edema. Effects in these patients can be minimized by lowering the daily dosage and administration in divided doses. Under these conditions, energizing effects may be delayed from two to three additional weeks, but a wider margin of safety exists.

Summary

Because of their antianginal and antidepressive actions, monoamine oxidase inhibitors provide appreciable benefit in 70 per cent of patients with cardiovascular disease. Increase in exercise tolerance is the most noteworthy effect. If treatment is individualized, side effects are few and easily counteracted.

References

1. Zbinden, G. and Studer, A. Experimental pathology of iproniazid and related compounds. *Ann. New York Acad. Sc.*, 80: 873, 1959.
2. Regelson, W., Hoffmeister, F. S. and Wilkins, H. Effect of iproniazid on survival in the dog, following acute coronary occlusion. *Ann. New York Acad. Sc.*, 80: 981, 1959.
3. Cesarman, T. Marsilid in the treatment of angina pectoris. *J. Clin. & Exper. Psychopath.*, 19: 169, 1958.
4. Cossio, P. The treatment of angina pectoris and other muscular pain due to ischemia with iproniazid and isoniazid. *Am. Heart J.*, 56: 113, 1958.
5. Crane, G. E. Clinical studies on the cardiovascular effects of Marsilid. *Angiology*, 11: 25, 1960.
6. Grauman, S. J. Small doses of iproniazid in the therapy of angina pectoris. *Am. J. Cardiol.*, 3: 544, 1959.
7. Master, A. M. Iproniazid (Marsilid) in angina pectoris. *Am. Heart J.*, 56: 570, 1958.
8. Nussbaum, H. E., Leff, W., Mattia, V. D., Jr. and Hillman, E. The effects of iproniazid phosphate (Marsilid) on hypertension. Preliminary report. *Angiology*, 8: 198, 1957.
9. Shoshkes, M., Rothfeld, E. L., Becker, M. C., Finkelstein, A., Smith, C. C. and Wachtel, F. W. Iproniazid in angina pectoris. A double-blind study. *Circulation*, 20: 17, 1959.
10. Wolffe, J. B. and Shubin, H. Treatment of angina pectoris with Nialamid. *Clin. Med.*, 6: 1563, 1959.
11. Schweizer, W. Isopropylhydrazides in angina pectoris. *Ann. New York Acad. Sc.*, 80: 1016, 1959.

Biochemistry of Monoamine Oxidase Inhibitors*

PARKHURST A. SHORE, PH.D.

Bethesda, Maryland.

WITH the increasing application of biochemical technics to pharmacologic research, there has been a rapid accumulation of knowledge concerning the biochemical effects of certain drugs which, in turn, has helped us to learn more of basic biochemical mechanisms. The advent of the monoamine oxidase (MAO) inhibitors represents an example of this. Let us consider some of the biochemical aspects of the MAO inhibitors as related to their pharmacologic effects and then point out the valuable information gained by their use.

BIOCHEMICAL CLASSIFICATION OF MAO INHIBITORS

In biochemical terms, MAO inhibitors can be classified into two types:

1. *Irreversible:* Examples of this type of inhibitor are those drugs which have been found clinically useful, compounds such as iproniazid, Catron,® nialamide and phenelzine. These drugs appear to exert a very persistent action which is not correlated with the level of drug in the tissues. Thus, iproniazid causes a blockade of MAO in rat tissues long after the drug has disappeared from the affected tissues.[1]

2. *Reversible:* Examples of this type of inhibitor are found in the harmine series. Harmaline, for example, has been found to be a fully reversible inhibitor as shown by a rapid reactivation of MAO as the drug leaves the tissues.[2] This type of inhibitor, unlike the iproniazid type, is relatively short-acting, and blockade of enzyme activity is dependent upon maintenance of drug levels in the tissues.

Since the irreversible inhibitors are the ones of clinical importance at this time, most of the biochemical and pharmacologic studies have been carried out with them.

STIMULATORY EFFECTS AND EFFECTS ON BRAIN AMINES

Administration of a single dose of a potent MAO inhibitor such as iproniazid or Catron® to rabbits causes an increase in the levels of brain serotonin and norepinephrine, but no obvious pharmacologic effects occur.[3,4] With daily administration of the inhibitors, even higher levels of the amines result, and a pronounced psychomotor activity and some peripheral sympathetic stimulation can be seen.

The pharmacologic effects appear to be more closely associated with the change in brain norepinephrine levels than serotonin levels since after withdrawal of the drug, the pharmacologic effects disappear when the norepinephrine, but not the serotonin levels, return to normal.[4]

The stimulatory effects of MAO inhibitors are seen most vividly when they are administered to animals which are then given the serotonin and catecholamine releaser, reserpine. Pretreatment of rabbits with a MAO inhibitor converts the usual depressant effect of reserpine to a strongly excitant effect.[5,6] Since the metabolism of the released amines is blocked by the MAO inhibitor, the freed amines exist in high concentration in the brain and cause central stimulation. Thus, the central pharmacologic effects of the MAO inhibitors appear to be closely associated with a high level of free brain amines.

ANTICONVULSANT EFFECTS

MAO inhibitors have been found to exert marked anticonvulsant actions in rats.[7] This effect, as well as the central stimulatory effect, appears to be closely associated with the rise in brain serotonin and norepinephrine levels. The inhibitors do not appear to act as anticon-

* From the National Heart Institute, Bethesda, Maryland.

vulsants *per se* but act rather through the action of the amines; since if serotonin and norepinephrine are released from the brain by prior treatment with reserpine no anticonvulsant effect of subsequently administered MAO inhibitors can be demonstrated.

Effects on the Cardiovascular System

The clinical cardiovascular effects of MAO inhibitors, postural hypotension and prevention of angina pain, have aroused considerable interest. The mechanisms involved in these effects are extremely difficult to elucidate because of the inability to reproduce them in laboratory animals. It should be kept in mind, however, that some of the amine substrates of MAO can affect the cardiovascular system. For example iproniazid has been shown to raise the circulating blood levels of serotonin[8,9] which has been reported to be a coronary vasodilator.[10]

Recently, it has been shown that perfusion of the superior cervical ganglia of dogs with high concentrations of MAO inhibitors blocks synaptic transmission.[11] Whether or not this effect bears a relation to the orthostatic hypotension seen in patients is problematic, since extremely high levels of the drugs are required in the perfusion fluid before the effect is seen.

Physiologic Studies

Investigations into the biochemistry of the MAO inhibitors have suggested possible mechanisms of some of the actions of these drugs, as described previously. Perhaps of greater fundamental importance is the insight into physiologic mechanisms that has resulted from studies with these drugs.

By the use of the MAO inhibitors we have learned that: (1) Serotonin has a remarkably rapid rate of synthesis in brain, about 50 per cent of brain serotonin turning over each ten to fifteen minutes.[12,13] This observation emphasizes the importance of serotonin in brain function. (2) Although other enzymes appear to play major roles in the metabolism of circulating catecholamines, MAO appears to be the enzyme of primary importance for controlling the levels of catecholamines as well as serotonin in brain.[14] (3) Use of MAO inhibitors has revealed other amine products of amino acid decarboxylation (tryptamine, for example) in the body, amines which had escaped detection previously because they are normally rapidly destroyed by MAO.[15]

Studies with the MAO inhibitors demonstrate to a high degree the usefulness and importance of a close liaison between clinical and laboratory investigations. We may look forward to further fruitful coordination of studies and interests.

Summary

The diverse biochemical and pharmacologic actions of the monoamine oxidase inhibitors have proved of great value in learning more of the importance of amines in the body. Investigations with these drugs have revealed the possible involvement of various amines in brain function and in the actions of these and other drugs on brain excitability and regulation of the cardiovascular system.

References

1. Hess, S., Weissbach, H., Redfield, B. G. and Udenfriend, S. The relationship between iproniazid metabolism and the duration of its effect on monoamine oxidase. *J. Pharmacol.*, 124: 189, 1958.
2. Udenfriend, S., Witkop, B., Redfield, B. G. and Weissbach, H. Studies with reversible inhibitors of monoamine oxidase: harmaline and related compounds. *Biochem. Pharmacol.*, 1: 160, 1958.
3. Spector, S., Prockop, D., Shore, P. A. and Brodie, B. B., The effect of iproniazid on brain levels of norepinephrine and serotonin. *Science*, 127: 704, 1958.
4. Spector, S., Shore, P. A. and Brodie, B. B. Biochemical and pharmacological effects of the monoamine oxidase inhibitors, iproniazid, 1-phenyl-2-hydrazinopropane (JB 516) and 1-phenyl-3-hydrazino-butane (JB 835). *J. Pharmacol.*, 128: 15, 1960.
5. Shore, P. A. and Brodie, B. B. LSD-like effects elicited by reserpine in rabbits pretreated with iproniazid. *Proc. Soc. Exper. Biol. & Med.*, 94: 433, 1957.
6. Pletscher, A. Wirkung von Isopropyl-isonicotinsäurehydrazid auf den Stoffwechsel von Catecholaminen und 5-Hydroxytryptamin im Gehirn. *Schweiz. med. Wchnschr.*, 87: 1532, 1957.
7. Prockop, D., Shore, P. A. and Brodie, B. B. An anticonvulsant effect of monoamine oxidase inhibitors. *Experientia*, 15: 145, 1959.
8. Shore, P. A., Gillespie, L., Spector, S. and Prockop, D. Increase in blood serotonin levels induced by iproniazid in man and rabbits. *Naturwissenschaften*, 45: 340, 1958.
9. Pletscher, A. and Bernstein, A. Increase of 5-hydroxytryptamine in blood platelets by isopropyl-isonicotinic acid hydrazide. *Nature*, 181: 1133, 1958.
10. Crumpton, C. W., Castillo, C. A., Rowe, G. G. and Maxwell, G. M. Serotonin and the dynamics of the heart. *Ann. New York Acad. Sc.*, 80: 960, 1959.
11. Gertner, S. B. Monoamine oxidase inhibitors and ganglionic blockage. *Fed. Proc.*, 18: 393, 1959.

12. Brodie, B. B., Spector, S., Kuntzman, R. and Shore, P. A. Rapid biosynthesis of brain serotonin before and after reserpine administration. *Naturwissenschaften*, 45: 243, 1958.

13. Udenfriend, S., Weissbach, H. and Bogdanski, D. F. Biochemical findings relating to the action of serotonin. *Ann. New York Acad. Sc.*, 66: 602, 1957.

14. Shore, P. A., Mead, J. A. R., Kuntzman, R., Spector, S. and Brodie, B. B. On the physiologic significance of monoamine oxidase in brain. *Science*, 126: 1063, 1957.

15. Oates, J. A. and Zaltzman, P. Discussion remarks at Symposium on Monoamine Oxidase Inhibitors. *Ann. New York Acad. Sc.*, 80: 977, 1959.

Storage of Catecholamines in the Heart*

Effect of Amine Oxidase Inhibitors

KYOHEI KAKO, M.D., ATHANASIOS CHRYSOHOU *and* RICHARD J. BING, M.D., F.A.C.C.

Detroit, Michigan

INTEREST of this laboratory in the relationship of catecholamines to heart muscle began with studies on the possible mechanism of the decline in mechanical efficiency of the isolated heart.[1] In the course of this work it became apparent that the heart in vitro can store catecholamines.[1a] This led to an investigation of the factors influencing storage and release of catecholamines of the heart in situ.

IN VITRO STUDIES

The decline in mechanical efficiency of the heart in the heart-lung preparation has been the subject of a large series of investigations. First observed by Starling, this decline has been thought to be the result of unfavorable mechanical conditions, of denervation of the heart and of the lack of essential hormone-like substances in the perfusion fluid.[2–4] Rein[5] discovered that when liver and spleen were included in the perfusion circuit of the heart-lung preparation, electrical stimulation of the splenic nerves resulted in an increased ability of the heart to tolerate the effects of myocardial anoxia. Pinnoti[6] discovered that the addition of the liver to the heart-lung preparation led to diminished oxygen consumption of the heart. Rein[5] as well as Schmier[7] believed that a humoral substance was released by the spleen which resembles a cardiac glycoside in action. Green and Nahum[8] claimed that extracts of nonsaponifiable fraction of the liver possess a positive inotropic effect. Grabe and Krayer[9] found that when the liver was permitted to stand at room temperature, extracts from the organ acquired properties which were thought to be the result of tyramine. Experiments were performed in this laboratory dealing with the mechanism of the decline in mechanical efficiency of the isolated heart and with a possible influence of liver and spleen on its mechanical efficiency.

Catecholamine Concentration in Perfusion Fluid; Effects of Liver and Spleen: It could be shown that in all likelihood the decline in mechanical efficiency of the heart was the result of a diminution of catecholamines in the perfusion fluid;[1] for example, one hour after isolation of the heart, the average norepinephrine concentration in the perfusate had declined from 2.0 to 0.46 μg./L. of plasma, that of epinephrine from 1.8 to 0.9 μg./L. of plasma. In contrast, the concentration of catecholamines in the muscle of the isolated heart itself differed little from that found in the heart *in situ* (0.42 μg. as compared to 0.56 μg./gm. of heart). Inclusion of the liver and spleen in the perfusion circuit did not result in increased work of the isolated heart; however, it did lead to a diminution in the myocardial oxygen consumption, and hence in an increase in myocardial efficiency.[1] This effect of liver and spleen was accompanied by a diminished rate of disappearance of catecholamines in the perfusion fluid, possibly by the release of this material into the perfusion fluid from these organs. This is consistent with the observation that the addition of small amounts of norepinephrine and dopamine also produced a fall in myocardial oxygen consumption accompanied by an increase in the efficiency of the heart.[1]

Catecholamines in Heart Muscle and Effects of Addition of DOPA: Probably the most significant observation made in these studies was the fact that the concentration of catecholamines in heart muscle after the addition of DOPA

* From the Department of Medicine, Wayne State University College of Medicine, Detroit, Michigan. This work was supported by U. S. Public Health Service Grant No. H-5043, The Life Insurance Medical Research Fund, The American Heart Association, Abbott Laboratories, The Tobacco Industry Research Committee and Hoffmann-La Roche Inc.

(dihydroxyphenylalanine) did not diminish and actually increased despite the onset of cardiac failure (1.53 μg./gm. of failing heart muscle as compared to 0.94). This suggested that stored catecholamines are without influence on the mechanical performance of the isolated heart. This became particularly apparent when dihydroxyphenylalanine (DOPA), a precursor of nonepinephrine, was added to the perfusion fluid. A marked inotropic effect on the heart followed, due to conversion of DOPA to dopamine and norepinephrine.[1] However, after thirty minutes cardiac work and heart rate had again declined and failure progressed rapidly, despite a marked increase in the concentration of catecholamines in heart muscle. This is further confirmation that the concentration of catecholamines in heart muscle is without influence on the mechanical efficiency of the heart. The finding of increased catecholamine concentration in heart muscle following the addition of DOPA is consistent with the results of von Euler and Udden[10] and Pletscher.[11]

Studies Carried Out in Vivo

Intravenous Infusion of DOPA and MAO Inhibitor: Experiments were performed on the closed chest dog to investigate whether storage of catecholamines could take place after intravenous infusion of DOPA alone and in combination with an amine oxidase inhibitor, iproniazid. In addition, the possible release of stored catecholamines in heart muscle by the action of nicotine, reserpine and an increase in the heart rate was investigated. Iproniazid (50 mg./kg. weight) was injected twenty-four hours prior to the infusion of DOPA. DOPA solution (25 mg./kg. weight) was then infused intravenously over a period of approximately sixty minutes. One hour after the termination of infusion the heart was removed and the catecholamine content was determined by means of ferrocyanide oxidation according to the method of von Euler.[12] The experiments revealed that the combination of iproniazid and DOPA resulted in a marked increase in catecholamine concentration of the heart muscle (from a control average of 0.56 μg./gm. to 1.4 μg./gm. of heart muscle). The injection of iproniazid or DOPA alone raised the myocardial catecholamine concentration to a much lesser extent (0.6 μg./gm. of heart muscle and 0.54 μg./gm. of heart muscle, respectively).

Intravenous Infusion of Norepinephrine: Raab and Gigee[13] reported that epinephrine and norepinephrine were selectively taken up by the heart and other vascular tissues when massive doses of these compounds were administered to cats or dogs. Von Euler,[14] on the other hand, did not find any significant changes in the catecholamine content of heart, spleen, kidney or skeletal muscle of the cat when large or small amounts of catecholamines were administered. Axelrod et al.,[15] using tritium-labeled beta DL-H^3 epinephrine of high specific activity, found that thirty minutes after infusion of this compound, the concentration of H^3 epinephrine in heart, spleen, adrenal and pituitary gland exceeded that of the plasma several-fold. Experiments from this laboratory in which the catecholamine concentration of heart muscle was investigated following the intravenous infusion of norepinephrine (0.1 to 0.5 mg./kg. weight) revealed only a slight increase in catecholamine concentration of heart muscle (0.73 μg./gm. of heart muscle as compared to 0.56 in the control series). The injection of iproniazid prior to the infusions of norepinephrine had no appreciable effect (0.65 μg./gm. of heart muscle).

Effect of Nicotine, Reserpine and Tachycardia: It had been previously shown that catecholamines stored in heart muscle can be released by the action of nicotine, reserpine or suprathreshold stimulation.[16–18] Since these results had been obtained on isolated preparations only, the influence of these factors on catecholamines of the heart *in vivo* was followed. Nicotine was infused in doses of 2 mg./kg. over a period of one hour. Tachycardia was produced by stimulation with an electrode placed in the right atrium through a catheter. The infusion of nicotine failed to alter the concentration of catecholamines in the heart muscle (0.64 μg./gm. of heart muscle). Heart rates of 300 beats per minute were also without effect (0.65 μg./gm. of heart muscle). In contrast, intravenous infusion of reserpine significantly lowered catecholamine concentrations (0.35 μg./gm. of heart muscle).

Reasons for Lack of Pharmacologic Effect of Stored Catecholamines: The high concentration of catecholamines in heart muscle observed after the combined injection of DOPA and amine oxidase inhibitors has been observed by Pletscher.[11] The finding that the catecholamines in the intact heart *in vivo* possess no pharmacologic activity deserves special emphasis. Three possible explanations may be offered: (1) The catecholamines are transformed

by O-methylation into normetanephrine which is physiologically inactive.[19] However, this explanation is unlikely, since both metanephrine and normetanephrine fail to fluoresce after oxidation with ferricyanide.[20] (2) The catecholamines are bound to proteins. Thus, it was postulated by Brodie and his co-workers[21] that both 5-hydroxytryptamine as well as catecholamines are bound to proteins and thus are protected against action of monoamine oxidase. (3) The catecholamines are contained in the granules of the cell and are liberated only during stimulation or under the influence of reserpine.[22] Similar conclusions were also reached by Blaschko and co-workers[23] and Schuman.[24]

Summary

Storage and release of catecholamines in the isolated heart and the heart *in vivo* were investigated.

The addition of DOPA to the perfusion fluid of a heart-lung preparation markedly increased the catecholamine concentration of the isolated heart. *In vivo*, the combination of iproniazid and DOPA had the same effect. Iproniazid alone failed to influence myocardial amine concentration.

Nicotine raised the catecholamine concentration in heart muscle; electrically induced tachycardia failed to lower the catecholamine content of the heart *in vivo;* reserpine caused a marked reduction.

The reasons for the absence of a pharmacologic effect of the stored catecholamines are discussed.

References

1. Kako, K., Choudhury, J. D. and Bing, R. J. Possible mechanism of the decline in mechanical efficiency of the isolated heart. *J. Pharmicol. & Exper. Therap.*, 130: 46, 1960.

1a. Kako, K., Chrysohou, A. and Bing, R. J. Factors affecting myocardial storage and release of catecholamines. *Circulation Res.*, in press.

2. Gauer, O., Kramer, K. Zur Frage der oxydationsteigernden Wirkund des Adrenalin am Warmbluterherzen. *Pflügers Arch.*, 242: 328, 1939.

3. Gollwitzer-Meier, K. and Kruger, E. Einfluss der Herznerven auf dem Gaswechsel des Warmbluterherzen. *Pflügers Arch.*, 240: 89, 1938.

4. Gremels, H. Über der Beziehungen des Kohlenhydratstoffwechseln zur Physiologie und Pharmakologie. *Arch. exper. Path. u. Pharmakol.*, 194: 629, 1940.

5. Rein, H. Die Beeinflussung von Coronar-oder Hypoxie-bedingten Myokardinsuffizienz durch Milz-Leber. *Pflügers Arch.*, 253: 435, 1951.

6. Pinnoti, O. L'influenza del fegato sul metabolismo energico del cuore. *Arch. fisiol.*, 42: 170, 1942.

7. Schmier, J. Findings of experimental work with regard to the "spleen-liver mechanism." In: Symposium on Liver Function. Pub. No. 4, Am. Inst. of Biol. Sc, p. 390, 1958.

8. Green, J. P. and Nahum, L. H. Effects of liver fractions on myocardial contractility. *Circulation Res.*, 5: 634, 1957.

9. Grabe, F. and Krayer, O. Beitrag zur Aufklarung der kreislanfwirksamen (Adrenalin Ahnlichen) Stoffe in Leber-extraction. *Klin. Wchnschr.*, 29: 1381, 1934.

10. von Euler, U. S. and Udden, P Increase in noradrenaline content of organs after administration of DOPA in the cat. *Experientia*, 7: 465, 1951.

11. Pletscher, A. Einfluss von Isopropyl-isonikotinsaurehydrazid auf der Katecholamingehalt des Myokards. *Experientia*, 14: 73, 1958.

12. von Euler, U. S. and Floding, I. Fluorimetric estimation of noradrenaline and adrenaline in urine. *Acta physiol. scandinav. suppl.*, 33: 118, 1955.

13. Raab, W. and Gigee, A. B. Specific avidity of the heart muscle to adsorb and store epinephrine and nor-epinephrine. *Circulation Res.*, 3: 553, 1955.

14. von Euler, U. S. Catecholamine content of various organs of the cat after injections and infusions of adrenaline and noradrenaline. *Circulation Res.*, 4: 647, 1956.

15. Axelrod, J., Weil-Malherbe, H. and Tomchick, R. The physiological disposition of H^3-epinephrine and its metabolite metanephrine. *J. Pharmacol. & Exper. Therap.*, 127: 251, 1959.

16. Burn, J. H. and Rand, M. J. Action of nicotine on the heart. *Brit. M. J.*, 1: 137, 1958.

17. Paasonen, M. K. and Krayer, O. The release of nor-epinephrine from the mammalian heart by reserpine. *J. Pharmacol. & Exper. Therap.*, 123: 153, 1958.

18. Furchgott, R. F., Gubareff, de. T. and Grossman, A. Release of autonomic mediators in cardiac tissue by suprathreshold stimulation. *Science*, 129: 328, 1959.

19. Evarts, E. V., Gillespie, L., Fleming, T. C. and Sjoerdsma, A. Relative lack of pharmacological action of 3-methoxy analogue of nor-epinephrine. *Proc. Soc. Exper. Biol. & Med.*, 98: 74, 1958.

20. Price, H. L. and Price, M. L. The chemical estimation of epinephrine and nor-epinephrine in human and canine plasma. II. A critique of the trihydroxyindole method. *J. Lab. & Clin. Med.*, 50: 769, 1957.

21. Brodie, B. B. and Shore, P. A. A concept for a role of serotonin and nor-epinephrine as chemical mediators in the brain. *Ann. New York Acad. Sc.*, 66: 631, 1957.

22. Sano,: Über den Zustand des Katecholamines in dem Zentral-Nerven Systems. *Klin. Wchnschr.*, 38: 57, 1960.

23. Blaschko, H., Hagen, P. and Welch, A. D. Localization of adrenaline in cytoplasmic particles of the bovine adrenal medulla. *Arch. exper. Pharmakol.*, 219: 17, 1953.

24. Schuman, H. J. The distribution of adrenaline and noradrenaline in chromaffin granules from the chick. *J. Physiol.*, 137: 318, 1957.

Pharmacologic Aspects of Monoamine Oxidase Inhibition*

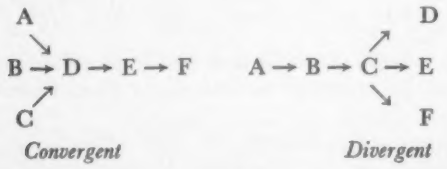
J. LEYDEN WEBB, PH.D.

Los Angeles, California

THE METABOLIC activities of living tissue depend upon reactions catalyzed by a great variety of enzymes which are not to be conceived as operating independently of each other. Certain groups of enzymes within cells function together to form a metabolic pathway, the product of one enzyme reaction being the substrate for the next enzyme in the pathway. Sometimes these functionally related enzymes occur as aggregates in structural units making for increased efficiency; the combination of oxidative enzymes in the mitochondria catalyzing the oxidation of pyruvate and the products of fatty acid oxidation via the tricarboxylic acid cycle is one example. On the other hand, occasionally the enzymes of a pathway may be distributed relatively homogeneously within the cell and the pathway is operative because of the specificity of the various enzymes for the intermediates. The normal cell possesses numerous pathways that are active simultaneously, and often these pathways are themselves interrelated and affect one another. There are simple linear pathways:

$$A \rightarrow B \rightarrow C \rightarrow D \rightarrow E$$

and there are those that branch; if two or more reactions lead into one sequence, this may be termed a *convergent pathway;* and if the product of a sequence can be metabolized by two or more reactions, this may be termed a *divergent pathway*.



Convergent *Divergent*

The metabolic system that we are to deal with is both convergent and divergent, in that several different amines, formed by the individual synthetic reactions, converge on monoamine oxidase, but these amines may also be acted upon by enzymes other than monoamine oxidase.

One of the primary tenets of biochemical pharmacology is that marked effects on cellular metabolism and function may be achieved by a specific block of one of the pathways, produced by inhibition of a component enzyme. We know now that the arsenicals depress the growth of trypanosomes and spirochetes by a block of an enzyme, pyruvate oxidase, which is necessary for the introduction of pyruvate into the tricarboxylic acid cycle. In the terminology of Sir Rudolph Peters, such an enzyme block may be called a *biochemical lesion*, in that it produces a defect in metabolism comparable to the anatomic disruption of a tissue in the more classical sense of the term. The action of disulfiram (Antabuse®) is similar. It inhibits specifically the aldehyde oxidase that disposes of the acetaldehyde normally formed from the oxidation of ethanol and the resultant disagreeable effects are due to the accumulation of the aldehyde that occurs when alcohol is ingested. In this case, a biochemical lesion has been established in the pathway of alcohol oxidation. Much of the effort directed toward the finding of a drug capable of selectively depressing tumor growth is aimed at producing such a block in a synthetic pathway involved in the formation of nucleic acids and proteins. The closest analogy, however, to our present subject is the inhibition of cholinesterase, whereby the accumulation of acetylcholine alters the functioning of various junctional regions at which this neurohormone is formed and released.

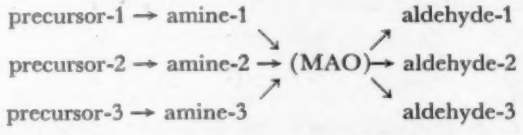
The monoamine oxidase (MAO) inhibitors, of which iproniazid (Marsilid®) is at present the type drug, act on one link in the pathway of

* From the Department of Pharmacology, School of Medicine, University of Southern California, Los Angeles, California.

amine metabolism. As a result of this action, the concentrations of the intermediates in this pathway are altered.[1,2] It so happens that some of these intermediates are pharmacologically very active. Epinephrine, norepinephrine, 5-hydroxytryptamine (serotonin), tryptamine, tyramine, dopamine and many other amines may be metabolized through this pathway. MAO catalyzes the oxidative deamination of these amines to the corresponding aldehydes. An over-all single sequence may be represented as:

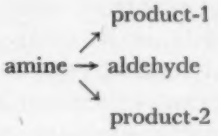
$$\text{precursor} \rightarrow \text{amine} \xrightarrow{\text{MAO}} \text{aldehyde} \rightarrow \text{products}$$

Each amine is formed by a particular synthetic process, which itself may be a pathway of several steps, but these reactions are not affected by the MAO inhibitors. The aldehydes formed are further metabolized by various routes. In the normal state the concentrations of amines and aldehydes in the cells are maintained at certain levels dependent on the relative rates of their formation and breakdown. When a block is imposed on MAO, all else remaining the same, the primary effect is to cause an increase in the amine concentration and a decrease in the aldehyde concentration until a new steady state is reached. It is most important to remember that the rate at which an amine will accumulate under these conditions is fundamentally dependent upon the rate at which it is being formed. Let us assume now that several different amines are being synthesized and released at different rates and all of these amines are metabolized by MAO:



If the MAO is inhibited, the amines will begin to accumulate but not necessarily at equal rates. If reaction-1 is faster than the others, amine-1 will build up rapidly and possibly reach much higher levels in the tissues than the other amines. Actually, it has been shown that MAO inhibition does result in the accumulation of a variety of amines at different rates and to various levels in the tissues. Of course, different tissues will not form exactly the same amines nor at the same relative rates, so that the pattern of amines in each tissue due to this biochemical lesion may be unique.

This metabolic picture is further complicated. MAO is not the only pathway for the metabolism of these amines.[3,4] Some amines are methylated on the ring hydroxyl group; some are oxidized or conjugated on the ring groups and in some the side-chain is cyclicized. Assuming several such pathways of degradation of a single amine, i.e.,



then what will happen when the MAO is specifically blocked may be readily visualized. If the MAO accounts for a large fraction of the amine metabolism, blockade will result in a steady rise of the amine concentration; but if this enzyme is a relatively insignificant pathway, its inhibition will not affect the amine level appreciably. Thus the accumulation of a particular amine will depend upon the importance of MAO in its disappearance. Of course, when MAO is inhibited, more of the amine is metabolized through the other pathways, as has been shown by analyzing the urinary products of amine metabolism after injection of the amines, both before and after MAO inhibition.[5–7] The complexity results from the fact that the various amines are metabolized at different rates through these pathways and great deviations in amine metabolism have been observed in the different tissues studied. Thus we must now conclude that the pattern of amine rise and distribution in the various tissues will depend upon the nature of the amines and the rates at which they are formed, and also upon the activity of the pathways by which the amines are metabolized and particularly by the role played by MAO.

To progress one step further, it is necessary to consider the actions of the amines by which the tissue function is altered. These various amines do not have identical pharmacologic activity. Some stimulate the central nervous system, some are depressant and some have little effect; some stimulate the heart rate and contractility markedly and others have no effect; some constrict blood vessels and some dilate them. In analyzing the pharmacologic effects of MAO inhibition, these different activities must be borne in mind. There are various views as to the amine responsible for a particular effect. For example, some believe that serotonin mediates the clinical effects of MAO inhibition, while others attribute this to norepinephrine or

to other amines. Present evidence does not warrant a definite conclusion concerning specificity of the amine. In the first place, in most of the cases studied MAO inhibition leads to accumulation of several amines to different degrees; it is certainly not legitimate to conclude that the effect is due to the one that rises to the highest level, because it may be much less pharmacologically active than another amine at lower concentration. In the second place, there are a number of amines in the tissues, of which we are as yet ignorant. Normally these amines occur at very low levels and could well play a major role when allowed to accumulate. It would appear that at the present time it is preferable to hold a position that the effects of the MAO inhibitors are responses to a new pattern of amine levels, not to any one amine.

Specificity of MAO Inhibitors: One might very well ask if these drugs are specific in their inhibition of MAO. In other words, can they also interfere with other enzymes in the body or act nonenzymatically? Although by no means all the known enzymes have been tested, it is true that the only enzyme found to be potently inhibited by iproniazid is MAO. Also the newer drugs that inhibit MAO seem in general to have the same basic effects as iproniazid. That is, there is some parallelism between the ability to inhibit MAO and to produce the characteristic pharmacologic or clinical responses. There is little or no evidence at any rate that the actions observed are due even in part to other mechanisms. However, the problem of the severe hepatocellular damage arises.[8] Is this a result of MAO inhibition? It could be that MAO in the liver functions in some manner in synthetic or detoxifying reactions upon which the integrity of the liver depends; but if so, these are unknown. It would also seem that some of the newer MAO inhibitors are not so prone to induce liver damage and yet they inhibit MAO quite potently. So it is possible that iproniazid is not absolutely specific and produces some of its effects, at least the toxic, by other mechanisms.

In this connection it is well to remember that these MAO inhibitors are metabolized in the tissues.[9] Iproniazid can be split enzymatically to isopropylhydrazine and isonicotinic acid, or by another enzyme system to acetone and isoniazid. It is quite possible that some of the toxic effects are related to these products rather than to the iproniazid itself. If this is true, one of the aims in the development of safer drugs would be to find potent MAO inhibitors that are relatively stable in the tissues or do not break down to toxic products. Nialamid (Niamid®) is perhaps a representative of this type of MAO inhibitor, since it is not appreciably broken down in the tissues and is excreted mainly unchanged.

Nature of MAO Inhibition: Turning to the nature of the inhibition itself, if a purified tissue extract of MAO is incubated with iproniazid, the MAO activity gradually falls over a period of half an hour to an hour. When the inhibited enzyme is then freed of the inhibitor in the surrounding medium by washing and dialysis for many hours, it is found that the activity does not return.[10,11] The inhibition is essentially irreversible. This is also observed in living tissue. A single large dose of iproniazid to an animal will bring about a slowly developing inhibition of MAO in the tissues; and when the MAO activity is followed, it is found that recovery of activity is very slow and occurs only after two to four weeks. It may well be that new active enzyme must be synthesized by the cells to replace the inactivated enzyme. This would be quite comparable to the situation when cholinesterase is irreversibly inhibited by the phosphorofluoridates such as diisopropyl-fluorophosphate (DFP). The reason for this irreversibility is probably that these inhibitors are structurally related to the normal amine substrates of the enzyme and enter into the enzymatic reaction in a similar manner. The fundamental grouping responsible for the MAO inhibition is the hydrazine moiety and a generalized inhibitor may be compared to a generalized substrate as follows:

substrate $R_1—CH_2—NH—R_2$

inhibitor $R_3—NH—NH—R_4$

The inhibitor combines with the enzyme just as the substrate does and begins to undergo the reaction that would normally split the —CH_2—NH— bond, but instead of completing this, the —NH—NH— group becomes chemically attached to the enzyme surface and cannot be split off. The enzyme in this sense can be said to be chemically inactivated.

Clinically Effective Dosage: Because of the prolonged inhibition, the question of a clinically satisfactory dosage schedule arises. In some respects it is similar to the problems in therapy with the digitalis glycosides. If an individual is started on a dosage of iproniazid of 100 to 150 mg. per day, the tissue MAO will be slowly

inhibited over one or two days to a level that is usually clinically manifest. If this same dosage is continued, the inhibition may proceed to levels higher than necessary or to complete inhibition. This is the expected result of drugs that exert a cumulative effect. To maintain the inhibition at a satisfactory level, it often suffices to give the patient only a maintenance dose of 10 to 25 mg. per day. That is, once the inhibition has been obtained, it is relatively easy to maintain it. Lower maintenance doses reduce the likelihood of side effects and serious toxic reactions. The rather high incidence of side effects when these drugs were first used is mainly attributable to the unnecessarily high doses used for maintenance. It might be thought that these smaller doses could be administered from the start and that the MAO inhibition would eventually reach the same levels as previously. This may be true, but clinically it has been observed that the best responses are obtained when the enzyme is not inhibited slowly. This may possibly be related to the ability of tissues to adapt to an inhibition when it progresses at a slow rate.

Differences among Various MAO Inhibitors: Finally, we may consider the problem of the differences among the various MAO inhibitors. If the hydrazine grouping is indeed the active portion of the molecules and if MAO inhibition is the primary mechanism by which the clinical effects are brought about, why are differences in action observed between these drugs? What is the function of the R_3 and R_4 groups attached to the hydrazine? For one thing, they control to some extent the potency of the MAO inhibition since they effect the binding of the inhibitor to the enzyme. But more important, they probably control the rates at which the drugs penetrate into the various tissues. This is particularly interesting with respect to the actions of these drugs on the central nervous system because of the peculiar nature of the permeability barriers to the brain. If it is assumed that the MAO's of the various tissues are equally susceptible to the MAO inhibitors (which is only approximately true), the degree of inhibition in a tissue would depend on the concentration of the inhibitor in that tissue. Differential effects upon the tissues could well be produced if the inhibitors penetrated into the cells of these tissues at different rates and to different degrees. Thus some MAO inhibitors, such as JB-516 (Catron), inhibit brain MAO rather readily, whereas others, including iproniazid, do not do this so specifically. Thus, the inhibitor molecule can be visualized as consisting of two parts: the enzyme-inhibiting portion and the carrier groups that determine how readily the drug enters into various tissues. Much of the advance in the developing of new drugs in this field has been in the attachment of carrier groups with special properties. Since some tissues accumulate amino acids, these amino acids have been used as carrier groups in the hope that they would lead to high concentrations of the drug in these tissues, but up to now the results have been disappointing, probably because the attachment of the amino acid to the hydrazine grouping destroys the ability to be selectively picked up by the tissues. If we knew in greater detail the mechanisms by which certain substances are concentrated by cells, particularly the metabolically linked active transport into cells, we could more rationally design new drugs; but at present our knowledge is vastly inadequate to these demands. Nevertheless, there is every reason to be optimistic about the possibilities of finding MAO inhibitors that will be, at least partially, selective in their action, not only with respect to the clinical target tissue but also with regard to the tissues from which the side effects derive. In a field such as this, it is safe to predict that in three years, the MAO inhibitors used clinically will not be those that are at present available but will be chosen from the hundreds of compounds now being examined in biochemical and pharmacologic laboratories. This is why it is more important to understand the general principles involved in MAO inhibition than to know a great deal of detailed information about the drugs now used.

Summary

The block of an enzyme, such as monoamine oxidase, may be simple but the effect of this block upon the tissue functions are clearly complex. The behavior of intracellular multienzyme systems is difficult to express kinetically and, in addition, the quantitative relationship between the tissue function and the concentration of an intermediate is generally unknown. In the present case the situation is complicated by the presence of multiple pathways: there are several pathways of amine formation, there are an unknown number of amines formed and there are different pathways for the elimination of these amines. This field of investigation is one that particularly requires the simultaneous

application of biochemical, physiologic and pharmacologic concepts at the most fundamental levels.

References

1. Biel, J. H., Drukker, A. E., Shore, P. A., Spector, S. and Brodie, B. B. Effect of 1-phenyl-2-hydrazinopropane, a potent monoamine oxidase (MAO) inhibitor, on brain levels of norepinephrine and serotonin. *J. Am. Chem. Soc.*, 80: 1519, 1958.
2. Brodie, B. B., Spector, S. and Shore, P. A. Interaction of monoamine oxidase inhibitors with physiological and biochemical mechanisms in brain. *Ann. New York Acad. Sc.*, 80: 609, 1959.
3. Blaschko, H. Amine oxidase and amine metabolism. *Pharmacol. Rev.*, 4: 415, 1952.
4. LaBrosse, E. H., Axrelrod, J. and Kety, S. S. O-methylation, the principal route of metabolism of epinephrine in man. *Science*, 128: 593, 1958.
5. Schayer, R. W. *In vivo* inhibition of monoamine oxidase studied with radioactive tyramine. *Proc. Soc. Exper. Biol. & Med.*, 84: 60, 1953.
6. Kirshner, N., Goodall, McC. and Rosen, L. The effect of iproniazid on the metabolism of dl-epinephrine-2-C^{14} in the human. *J. Pharmacol. & Exper. Therap.*, 127: 1, 1959.
7. Sjoerdsma, A., Lovenberg, W., Oates, J. A., Crout, J. R. and Udenfriend, S. Alterations in the pattern of amine excretion in man produced by a monoamine oxidase inhibitor. *Science*, 130: 225, 1959.
8. Kahn, M. and Perez, V. Jaundice associated with the administration of iproniazid. *Am. J. Med.*, 25: 898, 1958.
9. Koechlin, B. and Iliev, V. The metabolism of iproniazid. *Ann. New York Acad. Sc.*, 80: 864, 1959.
10. Zeller, E. A., Barsky, J. and Berman, E. R. Amine oxidases. XI. *J. Biol. Chem.*, 214: 267, 1955.
11. Davison, A. N. The mechanism of the irreversible inhibition of rat-liver monoamine oxidase by iproniazid (Marsilid). *Biochem. J.*, 67: 316, 1957.

The Mode of Action of Monoamine Oxidase Inhibitors with Special Reference to Serotonin

CHARLES W. CRUMPTON, M.D.
Madison, Wisconsin

SEROTONIN, ADRENALINE, noradrenaline, acetylcholine and histamine comprise a group of hormones which cause smooth muscles to contract, and each has been implicated in the normal functioning of the nervous system. The hormone is formed by a specific enzyme reaction, stored in some cellular particle, in which form it is pharmacologically inactive. For serotonin, one such particle is the platelet of the blood. When the hormone is released from this particle, it becomes pharmacologically active and able to cause muscular contraction or nerve activity. Once the hormone has acted upon its target cell, it must be disposed of in order to avoid a continuing effect that might be physiologically undesirable. For this purpose a destructive enzyme is provided. It is probably for this reason that one finds monoamine oxidase in smooth muscles and in nerves. This enzyme actively destroys serotonin, noradrenaline and adrenaline, which are monoamines. The result of inhibiting such a destructive enzyme is to allow accumulation and continuing action of the hormone on muscles and on nerves. The inhibition of an enzyme of this sort is thus one way of increasing the physiologically acting hormone in the body.[1]

The attempt to increase the amount of serotonin and the adrenalines arose largely from the suggestion of Woolley and Shaw.[2] These investigators produced considerable evidence to suggest that some mental disorders may arise from abnormalities in (probably a deficiency of) the serotonin content of the brain. They further suggested that perhaps a rational way to attempt treatment of these disorders would be to increase the serotonin content of the brain in order to make up the deficiency. This might be accomplished by increasing the production of the hormone or by inhibiting destruction of the hormone.

Beneficial effects in mental depression and angina pectoris have been observed in patients receiving monoamine oxidase inhibitor drugs. Evidence exists that monoamine oxidase inhibition does occur to a degree in patients receiving these compounds, but whether or not this is the specific mechanism by which these drugs exert their pharmacodynamic effect has not been established.

CARDIOVASCULAR EFFECTS OF MAO INHIBITORS

Well documented effects of monoamine oxidase (MAO) inhibitors upon the cardiovascular system in man and experimental animals have been described. Previous studies[3,4] have shown that iproniazid lowers the amplitude of myocardial contraction of the isolated perfused heart. This raises the question whether the action of the drug in angina pectoris is not due to a negative inotropic effect on the heart. Goldberg[5] studied the effects of several inhibitors on the cardiovascular actions of dopamine and tryptamine, in addition to those of norepinephrine and serotonin. After their cardiovascular actions were determined, an MAO inhibitor was administered intravenously. One hour after the inhibitor was given the amines were readministered as before.

These studies demonstrated that the cardiovascular actions of dopamine and tryptamine are potentiated and prolonged in the intact animal and that the effects of norepinephrine and serotonin are either not affected or diminished by prior administration of MAO inhibitors. The potentiation of dopamine and tryptamine ap-

* From the Cardiovascular Research Laboratory, University of Wisconsin Medical School, Madison, Wisconsin.

peared to correlate with MAO inhibition, but it was not known whether such potentiation was a simple enzymatic or more complex action of the inhibitors. Their results indicated that dopamine, tryptamine, tyramine and other as yet undiscovered potentiated amines should be considered along with serotonin and norepinephrine in evaluating the pharmacologic effects of MAO inhibitors.

Blood Pressure Effects: Biel[6] has reviewed the structure and activity relationships of monoamine oxidase inhibitors. Catron® (JB 516) in a dose of 50 mg./kg. administered to a dog will produce a blood pressure rise of one hour's duration. Sjoerdsma and co-workers[7] report that in a series of hypertensive patients Catron afforded a smooth lowering of blood pressure of the orthostatic type at a daily dosage of 25 mg. Hornykiewicz[8] has shown that iproniazid markedly enhanced blood pressure depression produced by dopamine in the guinea pig. It is conceivable that Catron might work via the same mechanism in producing a hypotensive effect in man.

A second possibility is that 2-phenylisopropylhydrazine may have a greater affinity for the cell receptor sites of the blood pressure–regulating centers than norepinephrine and thus block the pressor effects of the endogenous amine.[6] Zeller[9] has postulated an adrenergic blocking effect for iproniazid because of the similarity in "fit" of the hydrazide and epinephrine. Observations performed by Gertner[10] suggest that ganglionic block and amine oxidase inhibition may be related. Minz and Walaszek[11] have studied the effects of amine oxidase inhibitors on cerebrocortical responses to epinephrine. The amine oxidase inhibitors diminish the pressor response to epinephrine applied topically to the cerebral cortex of rabbits. The mechanism of the inhibitory response to cortically applied epinephrine is concerned with the catecholamine content of the hypothalamus since, when the content is normal, normal responses are obtained. When the content is lowered, as with reserpine or tetrabenzamine, there is an exaggerated cardiovascular response. When the content is raised, as with the amine oxidase inhibitors, schizophrenic serum or L-dopa, there is an inhibition of the cardiovascular responses.

Serotonin Metabolism and MAO Inhibition

One of the most important clinical effects of iproniazid and related compounds is stimulation of the central nervous system. This effect is thought to be related to an increase of serotonin and norepinephrine in the brain which results from amine oxidase inhibition.[12] Zbinden et al.[13] reported that decreased levels of 5-hydroxytryptamine found in guinea pig intestine following the administration of reserpine can be blocked by pretreatment with iproniazid. Granules in enterochromaffin cells made visible by histochemical technic disappear following the administration of reserpine but remain visible in pretreated animals, suggesting that iproniazid protects the 5-hydroxytryptamine in the enterochromaffin granules.

Scherbel[14] has reported that patients with rheumatoid arthritis manifest an exaggerated sensitivity to extravascular administration of serotonin and histamine. In an attempt to evaluate this problem clinically, Scherbel studied the excretion rate of serotonin metabolites in a patient with active rheumatoid arthritis following the intravenous administration of 2 mg. of 5-hydroxytryptamine-B-C^{14} creatinine sulfate containing 4 mc. of activity; a comparison was made of these rates and those of two normal control subjects. Before treatment approximately 10 per cent of the administered radioactive serotonin was excreted within five hours. After treatment for one month with 20 mg. daily of isocarboxazid, an analogue of iproniazid, 85 per cent of the radioactive serotonin was excreted within the same period (five hours). However, despite the increased excretion of serotonin metabolites, the ratio of 5-hydroxyindoleacetic acid to other metabolites remained the same within a twenty-four hour period before and after treatment, suggesting that monoamine oxidase was not completely inhibited or that some mechanism of action other than monoamine oxidase inhibition was responsible for this effect.[15]

Sjoerdsma, Gillespie and Udenfriend[7] attempted to ascertain whether drugs which, on the basis of studies on animals, are called monoamine oxidase inhibitors, do inhibit this enzyme in man in ordinary clinical dosage. The test was based on the conversion of orally administered serotonin to 5-hydroxyindoleacetic acid (5-HIAA), which is the end product of MAO activity on this amine. Following oral administration of 20 mg. of serotonin in a capsule, urine was collected for an eight-hour period and assayed for 5-HIAA. Normally, 80 to 90 per cent of the serotonin was excreted as 5-HIAA. The procedure was then continued during a

period when an MAO inhibitor was administered. Harmaline, Catron® and Marsilid® markedly reduced the conversion of serotonin to 5-HIAA in patients.

In interpreting these results, Sjoerdsma believed that only the inhibition occurring in the gut and possibly in the liver was being measured by the test. No increase in the level of blood serotonin could be found in several patients after ingestion of up to 50 mg. of serotonin, either in control status or during administration of Catron. In rats given 12 mg./kg. of serotonin by stomach tube, the blood level of the amine rose significantly but the concentration in the liver was unchanged from control values. If Catron (5 mg./kg.) was administered eighteen hours previously, a similar rise in the blood level was observed in one hour but, in addition, the concentration in the liver was about twice that of the controls; hence it appeared that only small amounts of serotonin given orally gain access to the systemic circulation. Additional experiments eliminated the possibility of poor absorption to account for marked degrees of inhibition. The MAO blockade induced by Catron was more effective in altering the metabolism of serotonin given orally.

The conversion of serotonin to 5-HIAA, as well as the blood pressure in the supine and upright position, were measured during short term therapy with this drug in nine hospitalized patients. Enzyme inhibition was demonstrated, together with a uniform and significant orthostatic lowering of the blood pressure. The authors state that, since almost all the MAO inhibitors currently available are hydrazines, it has been impossible thus far to separate clearly effects that are due to MAO inhibition from those that depend simply on the hydrazine group. Harmaline, a potent MAO inhibitor differing radically in chemical structure from the hydrazine compounds, was studied in an attempt to clarify this question.

In the five hypertensive patients studied there was a marked inhibition of serotonin metabolism to 5-HIAA in the absence of any significant effect on the blood pressure. Although this observation suggests that a decrease in blood pressure is not a necessary concomitant of MAO inhibition, the authors did not favor such a conclusion but stated that a gross correlation existed between MAO inhibition and hypotension with this group of compounds.

Although amphetamine and ephedrine are frequently referred to as MAO inhibitors, they showed relatively weak activity *in vitro* and were totally inactive in ordinary clinical dosage, as measured by Sjoerdsma's procedure.[7] Friend[16] reported a study of normal persons whose monoamine oxidase had been blocked with iproniazid in a dose of 3 mg./kg. of body weight for three days prior to an infusion of 600 μg. of norepinephrine; there was no difference in blood pressure values before and after the administration of iproniazid.

Neurovascular Effects of Serotonin

Page and McCubbin[17] suggested that serotonin may be a naturally occurring vasodilator compound important in vascular homeostasis, chiefly because of their demonstration of its ability to regulate peripheral neurogenic vasomotor tone. Maxwell et al.[18] studied the effect of serotonin on the systemic and coronary vascular bed of the dog. Total peripheral resistance decreased as a result of a significant reduction in mean arterial blood pressure. Coronary blood flow increased from 78 to 140 cc./100 gm./min. There was a significant rise in pulmonary artery pressure. In these experiments serotonin acted as a peripheral and coronary vasodilator and exhibited a vasoconstrictor effect upon the pulmonary vascular system.

To determine the effects of serotonin on peripheral blood pressure, Haddy et al.[19] infused serotonin into the brachial arteries of thirty-five dogs with forelimb vessels normal, constricted and dilated. They demonstrated that serotonin can be either a constrictor or a dilator and that it antagonizes extremes of neurogenically induced vascular tone. Their studies confirm the fact that serotonin may provide the body with a chemical buffering system. From these studies Haddy and his co-workers concluded that the irregular effect of serotonin upon arterial pressure may in part be related to the varying degree of neurogenic tone present at the time of administration.

Conclusions

In this report, experimental and clinical findings have been presented which may serve to elucidate the role of MAO inhibition in the pharmacologic and clinical actions of hydrazides. There is good evidence to show that, for certain central actions of hydrazides in animals (potentiation of monoamines and precursors, antagonism to reserpine and antiepileptic effect), MAO inhibition plays an important role.

Furthermore, within a series of hydrazide derivatives there is a rather good correlation between the influence on monoamine metabolism in animals and its clinical effects in humans (mental depression, angina pectoris, blood pressure regulation).[20]

It is apparent that dopamine, tryptamine, tyramine and other as yet undiscovered potentiated amines should be considered along with serotonin and norepinephrine in evaluating the pharmacologic effects of MAO inhibitors. In addition to the existence of different amines, there exist different pathways by which these amines can be metabolized or altered. Finally, the ability of the monoamine oxidase inhibitor to penetrate certain tissues and the resulting concentration in cells may determine the degree of block. These represent specific questions pertinent to the pharmacologic activity of MAO inhibitors which remain to be elucidated before the mechanism of the effects of these compounds is definitely known.

References

1. Woolley, D. W. Amine oxidase inhibitors; introductory remarks. *Ann. New York Acad. Sc.*, 80: 553, 1959.
2. Woolley, D. W. and Shaw, E. A biochemical and pharmacological suggestion about certain mental disorders. *Proc. Nat. Acad. Sc. U. S.*, 40: 228, 1954.
3. Allmark, M. G., Lu, F. C., Carmichael, E. and Lavalle, A. Some pharmacological observations on isoniazid and iproniazid. *Am. Rev. Tuberc.*, 68: 199, 1953.
4. Pletscher, A. and Pellmont, B. Biochemical and pharmacologic reactions of Marsilid on the heart. *J. Clin. & Exper. Psychopath.*, 19: 163, 1958.
5. Goldberg, L. I. Discussion of the paper by Randall, L. O. and Bagdon, R. E. Iproniazid and other MOA inhibitors. *Ann. New York Acad. Sc.*, 80: 639, 1959.
6. Biel, J. H., Nuhfer, P. A. and Conway, A. C. Structure and activity relationships of monoamine oxidase inhibitors. *Ann. New York Acad. Sc.*, 80: 568, 1959.
7. Sjoerdsma, A., Gillespie, L. and Undenfriend, S. A method for measurement of monoamine oxidase inhibition in man: application to studies on hypertension. *Ann. New York Acad. Sc.*, 80: 969, 1959.
8. Hornykiewicz, O. The action of dopamine on the arterial blood pressure of the guinea pig. *Brit. J. Pharmacol.*, 13: 91, 1958.
9. Zeller, E. A. Enzymologic effects of Marsilid and related hydrazine derivatives. *J. Clin. & Exper. Physiopath.*, 19: 32, 1958.
10. Gertner, S. B. Monoamine oxidase inhibitors and ganglionic block. *Fed. Proc.*, 18: 393, 1959.
11. Minz, G. and Walaszek, E. J. Effects of amine oxidase inhibitors on cerebral cortical responses to epinephrine. *Ann. New York Acad. Sc.*, 80: 617, 1959.
12. Shore, P. A. Possible mechanism of antidepressant action of Marsilid. *J. Clin. & Exper. Psychopath.*, 19: 56, 1958.
13. Zbinden, G., Pletscher, A. and Studer, A. Hemmung der Reserpin-Bedingten 5-Hydroxytryptamin-Freisetzung im Enterochromaffinen System durch Isopropyl-Isonicotinsaurehydrazid. *Klin. Wchnschr.*, 11: 565, 1957.
14. Scherbel, A. L. and Harrison, J. W. The effect of serotonin antagonists on the exaggerated response of serotonin in patients with rheumatoid arthritis and related diseases. *Clin. Res.*, 6: 401, 1958.
15. Scherbel, A. L. and Harrison, J. W. The effects of iproniazid and other amine oxidase inhibitors in rheumatoid arthritis. *Ann. New York Acad. Sc.*, 80: 820, 1959.
16. Friend, D. G. Discussion of paper by Sjoerdsma, A. et al.[7] *Ann. New York Acad. Sc.*, 80: 978, 1959.
17. Page, I. H. and McCubbin, J. W. The variable arterial pressure response to serotonin in laboratory animals and man. *Circulation Res.*, 1: 354, 1953.
18. Maxwell, G. M., Castillo, C. A., Clifford, J. E., Crumpton, C. W. and Rowe, G. G. Effect of serotonin (5-hydroxytryptamine) on the systemic and coronary vascular bed of the dog. *Am. J. Physiol.*, 197: 736, 1959.
19. Haddy, F. J., Emanuel, D. A., Gordon, P., Scott, J., Fleishman, M. and Lipton, M. Serotonin—an antagonist to extremes of neurogenic vasomotor tone. *J. Lab. & Clin. Med.*, 52: 816, 1958 (abstract).
20. Pletscher, A. Significance of monoamine oxidase inhibition for the pharmacological and clinical effects of hydrazine derivatives. *Ann. New York Acad. Sc.*, 80: 1039, 1959.

Theoretic Background of Therapy with Monoamine Oxidase Inhibitors in Cardiology*

GERHARD ZBINDEN, M.D.

Nutley, New Jersey

EXTENSIVE biochemical and pharmacologic investigations have shown that blockade of monoamine oxidase (MAO) markedly changes the metabolism of many biologic amines, and evidence has been accumulated that clinical effects observed with iproniazid and similar drugs are related to inhibition of this enzyme. We have studied hundreds of MAO inhibitors in our laboratories and over thirty compounds have been tested in humans by our clinical collaborators. From these investigations we conclude that all compounds which inhibit MAO *in vivo*, potentiate 5-hydroxytryptophan (5-HTP) and dihydroxyphenylalanine (DOPA), and block various reserpine effects, have a therapeutic action in depression, angina pectoris and on blood pressure.[1] However, many differences in the relative potencies of the various compounds were found and a close relationship between animal tests and efficacy in humans could not be established. Rate of absorption, speed of metabolism and organ distribution may explain some of the differences; but additional properties not related to MAO inhibition may also account for certain therapeutic effects. In this paper several of these factors which may be important for the cardiovascular response are discussed.

EFFECT ON BLOOD PRESSURE

Clinically, the hypotensive effect of the MAO inhibitors is different from all other blood pressure-lowering substances. It can be described as inconsistent, mostly orthostatic, slow in onset and slow in disappearance after cessation of therapy. MAO inhibitors are often effective in the most severe cases of hypertension and are markedly potentiated by chlorothiazide. There are marked differences in potency among the MAO inhibitors tested in man, and there is no relationship between MAO inhibition in animals and effect on blood pressure in man. After a single intravenous injection in animals, MAO inhibitors may cause transient fall in blood pressure (iproniazid)[2] or a marked pressor response (1-alanyl-2-isopropylhydrazine = Ro 4-1340[3] and β-phenylisopropylhydrazine [Catron®]),[4] but this is again not correlated with their effects during chronic administration in man or their enzyme-inhibiting properties. The mechanism of the blood pressure-lowering action in humans is not known and it is difficult to investigate because it cannot be reproduced in animal experiments. Several possibilities shall be reviewed briefly.

1. *Central Activity:* From animal experiments done by Schallek[5] in our laboratories we have no indication that MAO inhibitors depress the hypothalamus or the vasoconstrictor centers of the medulla oblongata. Thus, there is no reason to believe that the hypotension results from central depression of the vasomotor system.

2. *Inhibition of Carotid Sinus Baroreceptor Reflex:* In anesthetized dogs, intravenous injection of 100 mg./kg. iproniazid causes a slight depression of the carotid sinus reflex.[6] This observation indicates that the compound interferes with the blood pressure-regulating mechanisms. The effects of chronically administered MAO inhibitors on the carotid sinus reflex are presently under investigation.

3. *Ganglionic Blockade:* Based on clinical observations, several investigators believe that MAO inhibitors function as slow-acting ganglionic blockers.[7] Side effects sometimes observed with iproniazid, such as constipation,

* From the Biological Research Department, Hoffmann-La Roche Inc., Nutley, N. J.

TABLE I*

Compound	Inhibition of Ganglionic Transmission (μg./ml.)			Hypotensive Effect after Chronic Administration in Man
	Minimal	Partly	Complete	
Iproniazid	100		400	+
β-phenylisopropylhydrazine	10	20	50	+++
1-benzyl-2-trimethylacetylhydrazine (Ro 4-1634)		600		0
Isoniazid	No effect up to 400			

* Inhibition of ganglionic transmission after perfusion of the compounds through the isolated superior cervical ganglion of the cat[8-10] and effect on blood pressure in humans.

urinary retention and postural hypotension, also suggest a blocking effect on autonomic ganglia. In the intact animal no ganglionic blockade can be demonstrated. However, if MAO inhibitors are perfused through the isolated superior cervical ganglion of cats, marked blockade of ganglionic transmission occurs. A few compounds have been tested with this method by Gertner[8,9] and some results are summarized in Table I. β-phenylisopropylhydrazine, a potent hypotensive agent, inhibits ganglionic transmission at a low dose. Iproniazid, which is less potent clinically, also inhibits ganglionic transmission, but ten-fold higher doses are required. Tersavid® (1-benzyl-2-trimethylacetylhydrazine), although two to three times more active as an MAO inhibitor than iproniazid, clinically has practically no effect on blood pressure, and only a very weak effect on ganglionic transmission.[10] Isoniazid has no effect on ganglionic transmission and does not lower blood pressure in man. The data indicate that slow-acting ganglionic blockade may be involved in the mechanism of action of MAO inhibitors.

4. Postganglionic Blockade and Inhibition of Norepinephrine Release: No experimental evidence is available which would indicate that MAO inhibitors block postganglionic fibers. Catecholamine release after stimulation of sympathetic nerves has been found to be unimpaired.[11]

TABLE II*

Compound	Molarity of Compounds in the Bath Solution 0.005	0.001	0.002 (% Blockade of Epinephrine-induced Contraction)	Depression of Blood Pressure in Man
Iproniazid	100	25	0	+
β-phenylisopropylhydrazine	100	100	0	+++
1-(DL-N-acetylmethionyl)-2-isopropylhydrazine (Ro 4-1018)	0	—	—	+
1-DL-seryl-2-isopropylhydrazine monohydrochloride (Ro 4-1038/1)	25	10	0	+++
1-benzyl-2-trimethylacetylhydrazine (Ro 4-1634)	100	50	0	0
1-alanyl-2-isopropylhydrazine hydrochloride (Ro 4-1340)	50	20	0	++
2-ethyl-benz /f/ isoindoline phosphate (Ro 2-679/3)†	100	100	100	0

* Adrenergic blocking action of MAO inhibitors determined on isolated seminal vesicles of the rat[1] and effects of the compounds on blood pressure in man.
† Inhibits MAO only *in vitro*.

On the other hand, it has been demonstrated that the reserpine-induced catecholamine release from the adrenal medulla is blocked after pretreatment with various MAO inhibitors.[12] Thus, these compounds may, under certain circumstances, interfere with catecholamine release.

5. Adrenergic Blocking Effect: It has been known for a long time that iproniazid competes with norepinephrine at the receptor site of the smooth muscle in the blood vessels.[13] Many other MAO inhibitors are also adrenergic blocking agents (Table II). However, other derivatives which clinically induce marked hypotension are inactive or slightly active as adrenolytic agents.[1] This comparison, however, is based on *in vitro* experiments, and it may well be that some compounds are split in the organism, resulting in a change in their pharmacologic properties.

Recently, it has been shown that iproniazid changes the norepinephrine sensitivity of the vessels.[14] Rabbits were pretreated with the drug, and contractility of the aorta in response to norepinephrine was tested *in vitro*. Compared with untreated controls, the contraction of the aorta of iproniazid-treated animals was markedly depressed. This could be an adrenolytic effect, but it may also be due to an increased catecholamine content of the tissues.

Effect in Angina Pectoris

The experimental background for the effect of MAO inhibitors in angina pectoris is poor. Several sites and mechanisms of action have been proposed.

1. Stimulation of Central Nervous System: Some observers believe that the effect of MAO inhibitors in angina pectoris is due to psychostimulation,[15] and there is no question that the sense of well-being and elevation of mood frequently observed after administration of these drugs is part of their therapeutic action, in cardiac as well as in psychiatric patients. In animals, psychic stimulation can be measured by reversal of reserpine-induced depression, but no relationship could be established between clinically observed psychostimulation and relative potency in this test. Recently, Schallek[16] demonstrated for the first time electroencephalographic changes which suggest a stimulation of certain brain centers after repeated administration of iproniazid. It is planned to test other compounds in this experiment, and attempts will be made to correlate neurophysiologic effects and MAO inhibiting properties with clinically observed psychostimulation and antianginal effects.

MAO inhibitors also have central analgesic effects, and it has been suggested that their action in anginal attacks is due to an increased pain threshold.[17] There is not yet enough experimental and clinical evidence to substantiate this theory.

2. Coronary Dilation: Increased coronary flow has been demonstrated experimentally after intravenous administration of several MAO inhibitors.[18] It is unlikely that a similar mechanism is involved after chronic oral administration in man. Furthermore, increased serotonin content of the blood was found after repeated administration of MAO inhibitors in humans.[19] Serotonin is a coronary dilator substance[20] and it is possible that the antianginal effect is due to serotonin-induced coronary dilation. Unfortunately, no attempts have been made yet to correlate increased serotonin in the blood with the therapeutic effect in angina pectoris.

3. Effect on Pain Transmission: It has been speculated that the antianginal effect of MAO inhibitors may be due to a blocking of the neurohumoral pathway responsible for the transmission of cardiac pain. Up to the present, no experimental proof for this assumption has been found.

4. Oxygen-sparing Effect: There is some experimental evidence that MAO inhibitors may decrease the oxygen requirement of the tissues. Todd et al.[21] reported that experimentally induced anoxic tissue damages were partly prevented by pretreatment of the animals with iproniazid. It is also possible that the stimulating action of the catecholamines on the oxygen requirement of the heart muscle is counteracted by MAO inhibitors. In order to investigate this possibility, myocardial necroses were produced in rats by subcutaneous injections of isoproterenol. These alterations are thought to be due to increased oxygen consumption of the heart muscle.[22] After pretreatment with the MAO inhibitor isocarboxazid, extent and severity of the necroses were significantly reduced.[1,23] However, many more animal and clinical experiments are needed to substantiate whether MAO inhibitors really decrease oxygen requirement of the heart muscle.

Summary

In human subjects the main cardiovascular effects of the MAO inhibitors of the hydrazine type are orthostatic hypotension and decrease or abolishment of chest pain in angina pectoris. Site and mechanism of action are not yet known but various theories based on clinical and pharmacologic observations have been discussed. The hypotensive effect could be due to a slowly developing ganglionic or postganglionic blockade or be related to adrenolytic properties of the drugs. The therapeutic action in angina pectoris may be a consequence of central stimulation or blockade of pain transmission, but the possibility of an improvement of the myocardial metabolism, either by coronary dilatation or an influence on oxygen requirement of the heart muscle, has also been proposed.

References

1. Zbinden, G., Randall, L. O. and Moe, R. A. Clinical and pharmacological considerations of

mode of action of monoamine oxidase inhibitors. *Dis. Nerv. System* (suppl. 1), 21: 89, 1960.
2. Benson, W. M., Stefko, P. L. and Roe, M. D. Pharmacologic and toxicologic observations on hydrazine derivatives of isonicotinic acid (Rimifon, Marsilid). *Am. Rev. Tuberc.*, 65: 376, 1952.
3. Pletscher, A. Significance of monoamine oxidase inhibition for the pharmacological and clinical effects of hydrazine derivatives. *Ann. New York Acad. Sc.*, 80: 1039, 1959.
4. Horita, A. Pharmacology of JB 516 (PIH). *Ann. New York Acad. Sc.*, 80: 590, 1959.
5. Schallek, W. Personal communication.
6. Leusen, I. Discussion. *Ann. New York Acad. Sc.*, 80: 636, 1959.
7. Cesarman, T. Iproniazid in cardiovascular therapy, with special reference to its action in angina pectoris and blood pressure. *Ann. New York Acad. Sc.*, 80: 988, 1959.
8. Gertner, S. B. Ganglionic block and monoamine oxidase inhibitors. *Nature*, 183: 750, 1959.
9. Gertner, S. B. Monoamine oxidase inhibitors and ganglionic block. *Fed. Proc.*, 18: 393, 1959.
10. Gertner, S. B. Personal communication.
11. Brown, G. L. and Gillespie, J. S. The output of sympathetic transmitter from the spleen of the cat. *J. Physiol.*, 138: 81, 1957.
12. Zbinden, G. and Studer, A. Histochemische Untersuchungen über den Einfluss von Iproniazid (Marsilid) auf die durch Reserpin erzeugte Freisetzung von Adrenalin und Noradrenalin aus dem Nebennierenmark. *Experientia*, 14: 201, 1958.
13. Griesemer, E. C., Dragstedt, C. A., Wells, J. A. and Zeller, E. A. Adrenergic blockade by iproniazid. *Experientia*, 11: 182, 1955.
14. Bächtold, H. P. and Pletscher, A. Abschwächung der Noradrenalin-Wirkung auf die isolierte Aorta bei Hemmung der Monoaminoxydase. *Experientia*, 15: 265, 1959.
15. Master, A. M. Iproniazid (Marsilid) in angina pectoris. *Am. Heart J.*, 56: 570, 1958.
16. Schallek, W. Neurophysiological studies with monoamine oxidase inhibitors. *Dis. Nerv. System*, (suppl. 1), 21: 64, 1960.
17. Emele, J. F., Shanaman, J. E. and Warren, M. R. Analgesic activity of monoamine oxidase inhibitors. *Fed. Proc.*, 18: 387, 1959.
18. Pellmont, B. and Pletscher, A. Experimenteller Beitrag zur Wirkung von Isopropyl-isonicotinsäurehydrazid auf Herz und Kreislauf. *Helvet. physiol. et pharmacol. acta*, 16: C25, 1958.
19. Pletscher, A. and Berstein, A. Increase of 5-hydroxytryptamine in blood platelets by isopropylisonicotinic acid hydrazide. *Nature*, 181: 1133, 1958.
20. Crumpton, C. W., Castillo, C. A., Rowe, G. G. and Maxwell, G. M. Serotonin and the dynamics of the heart. *Ann. New York Acad. Sc.*, 80: 960, 1959.
21. Todd, L., Villareal, H. and Pisanty, J. Iproniazida en la anoxia tisular. II. Congreso Nacional de Ciencias Fisiologicas (abstracts) p. 103, 1959.
22. Rona, G., Chappel, C. I., Balazs, T. and Gaudry, R. An infarct-like myocardial lesion and other toxic manifestations produced by isopropylarterenol in the rat. *Arch. Path.*, 67: 443, 1959.
23. Zbinden, G. Inhibition of experimental myocardial necrosis by the monoamine oxidase inhibitor isocarboxazid (Marplan). *Am. Heart J.*, 60: 450, 1960.

Experimental and Clinical Effects of Amine Oxidase Inhibitors

A Seven Year Clinical Investigation of over 2,000 Patients*

ARTHUR L. SCHERBEL, M.D.

Cleveland, Ohio

SINCE THE introduction of isoniazid eight years ago as an antituberculosis agent[1] much experimental research and clinical investigation have been carried out to determine the biochemical and physiologic mechanisms by which this drug and related compounds produce their effects. It is apparent, however, from the increasing number of reports appearing in the medical literature, that the many effects resulting from administration of these substances by various routes are probably not all due to selective inhibition of monoamine oxidase.[2] It has been shown that they inhibit other enzymes, including choline esterase, decarboxylase and transaminase, and that they increase the utilization of pyridoxine. Furthermore, it is likely that alterations in enzymes or in endogenous substrates of a particular enzyme occur in certain diseases and that this may result in variation of pharmacologic action and clinical response to therapy. The multiple clinical effects which result from these drugs influence many systems of the body; perhaps the most significant are the effects on the central nervous system and on mesenchymal tissue.

My associates and I first started to investigate these compounds in 1953.[3] Since then, more than 2,000 patients with various diseases have been treated with fourteen different amine oxidase inhibitors alone or in combination with other therapeutic agents. More than 1,400 of these patients had a connective tissue disorder; others had depressive reactions alone or in combination with another disease, essential hypertension, malignancy, angina pectoris, Raynaud's phenomenon, sarcoid, tuberculosis, a variety of skin disorders and miscellaneous diseases. Length of treatment of these patients has varied from a few days to as long as five years.

The purpose of this paper is to discuss certain observations regarding the clinical use of these drugs and to correlate some experimental results with important therapeutic effects which are not generally well known.

EFFECTS ON THE NERVOUS SYSTEM

One of the most dramatic effects of amine oxidase inhibitors is stimulation of psychomotor activity. This does not occur consistently in all depressive states, at least not with dosages considered safe for long-term administration. It is also interesting that psychomotor stimulation may not occur in many patients who do not have a depressive reaction and who receive one of these drugs for another condition. Psychomotor stimulation is not a selective action; other central effects which are likely to occur include alteration in function of the autonomic and peripheral nervous systems. A blocking action involving some parts of the autonomic nervous system occurs coincident with antidepressant activity. This effect is manifested by postural hypotension which may vary in severity. Constipation may be the first manifestation suggesting involvement of the autonomic nervous system. Other effects include dryness of the mouth, urinary hesitancy, visual disturbances, decreased sweating, flushing, increased warmth of the limbs and alterations in sexual function.

An increased threshold to certain types of pain may develop coincident with alteration in autonomic nervous system activity. The pain of rheumatoid arthritis is lessened; it is not known whether this is due to an actual decrease in

* From the Department of Rheumatic Disease, The Cleveland Clinic Foundation and The Frank E. Bunts Educational Institute, Cleveland, Ohio.

pain or to an increased tolerance to the same pain stimulus. We have observed a similar reaction in patients with painful malignancy in whom the need for opiates is usually decreased. It is possible that a similar mechanism is responsible for lessening or disappearance of anginal pain.

Other effects originating in the central nervous system include hyperreflexia and muscle fasciculations which may occur with overdosage of these drugs.

The numerous effects of these drugs on various parts of the central nervous system do not occur consistently in all patients. This depends in part on the state of the central nervous system before therapy is started. Antidepressant activity is more likely to occur when psychomotor retardation pre-exists; it is less likely to appear in the presence of a normal psychomotor state. Similarly, the effect of amine oxidase inhibitors on blood pressure is more pronounced in patients with essential labile hypertension than in patients with normal blood pressure. Some types of pain are lessened or may disappear when other clinical signs of autonomic nervous system involvement appear, yet it is well known that these drugs do not possess analgesic properties.

Effect on Mesenchymal Tissue

In addition to the central effect of amine oxidase inhibitors on the nervous system, there is a peripheral action on mesenchymal tissue. The pharmacologic action responsible has not yet been determined. We have performed experimental and clinical studies which indicate that the action is a direct local effect of the drug which results in stimulation of fibroplasia in addition to lessening of inflammation. Experimentally in rats a significant increase in fibroplasia has been observed in implanted Ivalon® sponge, as compared to control animals.[4] The clinical counterpart of these experiments is apparent in the local treatment of patients with painful ischemic ulcers complicating Raynaud's phenomenon,[5] or with ulcerations, sinuses and fistulas complicating rheumatoid arthritis or chronic ulcerative colitis. We have also noted healing of certain persistent rectal sinuses occurring as complications of rectal surgery. In most instances, healing begins within one or two days after therapy is started and continues gradually and progressively. Occasionally we have observed no apparent response to this form of therapy. It is not known whether local amine oxidase inhibition occurs in peripheral mesenchymal tissue or whether another unrelated pharmacologic action is responsible for this effect.

Drug Potentiation

The action of numerous unrelated drugs is potentiated by the amine oxidase inhibitors; these include general and local anesthetic agents, barbiturates, thyroid, corticosteroids, ganglionic blocking agents, morphine, derivatives of atropine and the 4-aminoquinoline compounds, chloroquine phosphate and hydroxychloroquine sulfate. We have observed that chlorothiazide and hydrochlorothiazide potentiate the central nervous system effects of the amine oxidase inhibitors; this effect is characterized primarily by further psychomotor stimulation or an increase in postural hypotension. In animals, Shore and Brodie[6] have reported that the effect of reserpine may be altered from that of sedation to excitement if the animal is pretreated with an amine oxidase inhibitor. We have also observed this phenomenon in patients.

Dosage

The various hydrazine amine oxidase inhibitors currently available are here compared as to dosage and recommended administration.

Marsilid® (iproniazid).* The initial dose should never exceed 50 mg. daily and this amount is reduced as increased psychomotor activity appears. The maintenance dose varies between 5 and 25 mg. daily. If satisfactory improvement does not appear with this dosage schedule, other treatment should be tried.

Marplan® (1-benzyl-2-(5-methyl-3-isoxazolylcarbonyl) hydrazine)† has greater activity than iproniazid both *in vitro* and *in vivo*. Clinical response is apparent at lower doses and usually 20 to 30 mg. daily in single or divided doses are administered for a few days, after which time the daily maintenance dose is reduced to 10 mg. or less.

Catron® (β-phenylisopropyl hydrazine)‡ is one of the most potent hydrazine monoamine oxidase inhibitors currently available. The initial dose is usually 6 to 9 mg. daily. Occasionally 12 mg. daily are administered initially but this amount should be reduced within two to

* Supplied through the courtesy of Hoffmann-La Roche, Inc.

† Supplied through the courtesy of Hoffmann-La Roche, Inc.

‡ Supplied through the courtesy of Lakeside Laboratories.

our weeks. The usual maintenance dose varies between 3 and 6 mg. daily. In some patients, the maintenance dose can be reduced further to 3 mg. given on alternate days.

Nardil (phenylethylhydrazine)* is somewhat less active clinically than Marplan or Catron and causes less effect on the autonomic nervous system, i.e., there is less postural hypotension and constipation; consequently the initial dose is greater, usually 15 mg. two or three times daily. Occasionally the maintenance dose can be reduced to 10 mg. or even 5 mg. daily.

Niamid® (nialamide)† is the least active of compounds now available. The initial dose varies between 100 and 200 mg. daily for two to four weeks. The dose is gradually reduced and maintained between 50 and 100 mg. daily.

Response to Amine Oxidase Inhibitors

It is unlikely that monoamine oxidase inhibition is specific for any disease or that any cure will result from the administration of these compounds; improvement usually persists only while drug therapy is maintained, unless the course of the disease becomes altered by some other unknown factors. In certain chronic diseases, such as rheumatoid arthritis, it is possible, but unproved, that long-term therapy resulting in symptomatic improvement will favorably alter the natural course of the illness. In severe or progressive disease (depression, angina pectoris, rheumatoid arthritis and essential hypertension), response to a monoamine oxidase inhibitor is usually unsatisfactory even when large doses of the drug are administered. This incomplete response indicates that monoamine oxidase regulation alone is insufficient to reverse these diseases.

When the monoamine oxidase inhibitors are being administered, it is important to remember that the dose may vary for individual patients and that there may be a cumulative effect. After studying fourteen different compounds for more than seven years in over 2,000 patients, we believe that toxic reactions result from overdosage rather than from drug sensitivity. We have now observed a number of patients who require only very small doses of a monoamine oxidase inhibitor to maintain a therapeutic effect, and we have never observed a patient with signs of toxicity who was not hyperactive. It is also important to remember that side effects or drug toxicity disappear slowly and may persist for two to four weeks after medication is discontinued.

* Supplied through the courtesy of Warner-Chilcott Laboratories.

† Supplied through the courtesy of Pfizer Laboratories.

Clinical Indications for Monoamine Oxidase Inhibitors

At present, general agreement is lacking as to indications for the use of a monoamine oxidase inhibitor. Much more experimental and clinical investigation is needed before definite conclusions can be reached. Some authorities recommend that these drugs be used only when severe disease is present, because of their potential danger. Nevertheless, it is well known that patients with less serious disease respond more satisfactorily to smaller, adequately controlled doses of the drugs, without experiencing any toxic effects.

Depressive States: These drugs have been found effective in most types of depression, although severe endogenous depression and depressive reactions associated with cerebral arteriosclerosis usually do not respond satisfactorily. Psychiatrists who are familiar with these drugs have reported satisfactory improvement in 60 to 80 per cent of patients treated. When response to treatment is unsatisfactory, it is advisable not to increase the dose of an amine oxidase inhibitor, but rather to supplement it with other accepted measures of therapy, including electroshock therapy or the simultaneous administration of a second psychotropic drug which does not inhibit monoamine oxidase.

Rheumatoid Arthritis and Related Disorders: These diseases are characterized by involvement of the central nervous system and the mesenchymal tissue, but the relationship between these systems has not been clearly defined. Depression, emotional instability, alterations in function of the autonomic nervous system, poor resistance to stress, alterations in deep reflexes and various types of pain relieved by interruption of sympathetic nerve impulses occur commonly in these patients, but these manifestations are often overlooked or disregarded in favor of the more obvious and objective signs of inflammation and fibrosis in mesenchymal tissue. Administration of small doses of a monoamine oxidase inhibitor often results in alleviation of many of the central nervous system manifestations. Simultaneous administration of a monoamine oxidase inhibitor with a small dose of a corticosteroid or a 4-aminoquinoline compound such as chloroquine phosphate (Aralen®) or

hydroxychloroquine sulfate (Plaquenil®) usually results in a greater suppression of the mesenchymal reaction for long periods with less likelihood of serious relapse of the disease. When improvement occurs and persists, the drugs can be withdrawn in an orderly fashion.[3,7]

Angina Pectoris: Pain relief may occur in patients with angina pectoris following administration of amine oxidase inhibitors but this is not a consistent observation. Significant alteration in blood flow or of consumption of oxygen by the heart muscle is not apparent clinically or experimentally. Great care in dosage regulation is necessary to avoid serious postural hypotension or excessive psychomotor stimulation which might be detrimental. If relief of anginal pain is related to interruption of sympathetic nerve impulses, it is important to remember that psychomotor stimulation and postural hypotension may occur simultaneously.

Hypertension: All of the available monoamine oxidase inhibitors are capable of causing postural hypotension, although some compounds exert a greater effect on blood pressure than others. Marsilid, Catron and Marplan are more potent in this respect than Nardil and Niamid. This postural fall in blood pressure occurs simultaneously with increased psychomotor stimulation. In addition, other symptoms related to blockage of autonomic nervous system activity may occur.

During the past seven years, seventy-six patients with essential hypertension of varying severity and duration have been studied. Another group of eighteen patients (eight with rheumatoid arthritis, five with progressive systemic sclerosis and five with arteritis) with associated hypertension have been observed while receiving one of the amine oxidase inhibitors. Initially all patients had normal urea clearance. In fifty-three of the seventy-six patients with stage I or stage II disease (Keith-Wagener[5] classification), a significant fall in blood pressure occurred between the third and seventh day of therapy. Nevertheless, medication was eventually stopped in eleven of these patients because of side effects which included vascular headaches, excessive constipation, insomnia or increased psychomotor activity. Unilateral or bilateral edema of the lower limbs occurred in four patients. This did not appear to be related to cardiac or renal disease and disappeared quickly with simultaneous administration of chlorothiazide or hydrochlorothiazide. In each instance in which an oral diuretic was administered, the effect of the amine oxidase inhibitor was increased, i.e., postural hypotension or psychomotor activity was augmented. In the remaining forty-two patients who tolerated the drug, the blood pressure was difficult to maintain at a consistent decreased level in twenty-two patients. Dosage was changed at almost every visit. When the dose of medication was increased, the fall in blood pressure was unpredictable; when the dose was decreased, pressure frequently rose to pre-treatment levels.

In twenty-three of the seventy-six patients with more advanced hypertensive disease, side effects were apparent in nine, necessitating discontinuation of the drug, and seven patients were difficult to control without frequent adjustments of medication. Seven patients were easily controlled without additional therapy for two or more years.

In summary, twenty-seven of seventy-six patients with essential hypertension responded satisfactorily to an amine oxidase inhibitor, without side effects. Medication was stopped in twenty patients because of undesirable side effects. The combination of an amine oxidase inhibitor and chlorothiazide or hydrochlorothiazide was administered to ten patients with satisfactory control of blood pressure, and in nineteen patients, response to this therapy was not significant.

In two of five patients with progressive systemic sclerosis and associated hypertension, malignant hypertension eventually developed and they died, despite the administration of an amine oxidase inhibitor before the hypertension became advanced.

Side Effects

Side effects of the monoamine oxidase inhibitors are difficult to define, inasmuch as the pharmacologic actions are widespread within and without the central nervous system. A desirable effect occurring in one disease may be considered an undesirable side effect in another.

Besides psychomotor stimulation, postural hypotension, alleviation of ill-defined pain syndromes related to the autonomic nervous system, stimulation of mesenchymal fibrosis and drug potentiation which are considered desirable pharmacologic actions, other effects may occur, including vascular headaches of variable severity, flushing, perspiration of the upper part of the body, lightheadedness, vertigo, postural hypotension, nausea, constipation, anorexia,

increased appetite, urinary hesitancy, alteration in sexual activity, muscle fasciculations, hyperreflexia, clonus and unilateral or bilateral edema of upper or lower limbs.

These effects occur less frequently with Niamid; however, when the dosage is increased, there is no greater selectivity of action with this compound than with the others. When side effects occur from overdosage, they may persist for two to four weeks after the drug is withdrawn.

Toxic Effects

Toxicity reactions are rare when dosage recommendations are followed and patients are observed regularly for any cumulative effect of the drugs which may eventually result in overdosage.

Liver Damage: The most serious complication is acute liver necrosis; this has been observed primarily after the administration of Marsilid. It is likely that this complication is directly related to dosage, which varies with the individual patient. It is also important to emphasize that there is great variation in drug cumulation which may not become apparent for weeks or months. Overdosage from drug cumulation may appear relatively quickly after a relatively long latent period, during which response to dosage appears satisfactory.

It is well known that jaundice following the administration of Marsilid may run a fulminant course, with death occurring in 20 to 25 per cent of those afflicted.[9] With reduction in the dosage of Marsilid and the advent of newer, potentially less toxic amine oxidase inhibitors, the incidence of jaundice and the fulminating course associated with hepatic involvement have been significantly reduced.[10] It should be emphasized, however, that all these compounds are hydrazine analogues of Marsilid and are potentially capable of producing this complication.

It is apparent also that a rise in SGO transaminase does not always indicate impending liver damage. During a period of two years, ten of 546 patients in whom this determination was done at six-week intervals were found to have an elevation of serum transaminase three to eighteen months after beginning treatment. In each instance, the patient was called back for further liver function studies within seven to ten days after elevation of serum transaminase was first observed. Complete studies of liver function, including repeated determination of serum transaminase, yielded normal results, suggesting that transient elevation of transaminase may occur and return to normal without reflecting serious liver damage.

Toxic psychosis of mild degree has been observed in three patients who were over sixty years of age and exhibited senile changes resulting from cerebral sclerosis. Mental changes consisted of confusion, agitation, visual and aural hallucinations of mild degree and of temporary duration. Mental clearing was complete within three to five days after medication was stopped. Dosage of the amine oxidase inhibitor in two of these patients was thought to be excessive when symptoms became apparent.

Blood Dyscrasia: Unexplained anemia, normocytic and normochromic, has been noted in approximately 6 per cent of patients receiving an amine oxidase inhibitor. Bone marrow and hematologic studies have not been helpful in determining the cause. These compounds are chelating compounds, and it is possible that iron or another metal is bound and prevented from entering into the normal production of hemoglobin.

Leukopenia has been observed in three of our patients. One was receiving Catron and two were receiving Niamid. Bone marrow studies obtained in two patients were normal. Total leukocyte counts did not drop below 2,000 per cu. mm., and all three patients recovered uneventfully when medication was discontinued.

Skin Rash: In rare instances, patients taking a monoamine oxidase inhibitor may have a maculopapular skin rash which disappears promptly when medication is stopped.

Comments

The use of monoamine oxidase inhibitors as therapeutic agents in various diseases is an innovation in medicine which is in need of further clarification before definite conclusions can be drawn. Since these are potent drugs which inhibit monoamine oxidase irreversibly, much depends on the physician's skill, judgment and understanding of the activities of the drugs in achieving optimal results. Under no circumstances should these drugs be administered in doses considered excessive for the individual patient concerned. Conversely, the dosage must be adequate to obtain the maximum desired therapeutic effect. When the disease is severe, regardless of whether it is depression, rheumatoid arthritis, angina pectoris or essential hypertension, it is probable that satisfactory improvement will not result from the administra-

tion of an amine oxidase inhibitor as the sole therapeutic agent in doses safe for long-term administration. In these instances, every effort should be made to take advantage of the potentiating effect of these drugs on other drugs suitable for these patients.

The indications for the use of these drugs are somewhat paradoxic and further search for compounds with more selective effect is necessary. The stimulating action on the central nervous system, which is one of the early and primary pharmacologic effects of all the drugs so far investigated, is desirable in depression and in diseases, such as rheumatoid arthritis, frequently associated with depression. In angina pectoris and essential hypertension, however, psychomotor stimulation may be undesirable. Furthermore, the postural hypotensive effect may be undesirable in some patients with angina pectoris.

Drug potentiation has not been adequately emphasized as a desirable feature of these drugs. More effort should be made to take advantage of this reaction in patients with severe disease. In severe depressive states, initial electroshock therapy may be advantageous. The simultaneous administration of other antidepressant drugs which do not inhibit amine oxidase, together with the monoamine oxidase inhibitors, also has been highly effective in our hands. In patients with rheumatoid arthritis, the corticosteroids and the antimalarial compounds, chloroquine phosphate and hydroxychloroquine sulfate, can be administered with an amine oxidase inhibitor in smaller doses than usual with significantly greater therapeutic response.[11,12] In patients with terminal carcinoma, the need for opiates is usually greatly reduced when an amine oxidase inhibitor is administered.

The local application of an amine oxidase inhibitor usually results in healing of the lesion in patients with chronic fistulas or ulceration occurring as complications of chronic ulcerative colitis. In patients with hypertension the postural hypotensive effect is significant, but blood pressure control is often unpredictable and associated with side effects. The combination of reserpine and an amine oxidase inhibitor may result in increased mental excitation and is not recommended. The combination of chlorothiazide or a related compound potentiates the amine oxidase inhibitors; when this combination is used, dosage should be carefully regulated.

It has often been emphasized that because of the potential danger, the amine oxidase inhibitors should be used only in patients with more serious illness who have not responded to the usual routine therapeutic measures. We have not adhered to this concept completely, inasmuch as the larger doses of the drugs needed in such cases will be more likely to produce side effects or possibly toxic reactions. Patients with less serious disease frequently respond very quickly to small doses of the drugs, so that a complicated therapeutic program often is unnecessary.

Our experience indicates that the monoamine oxidase inhibitors have been effective in relieving many of the symptoms and even altering many of the tissue changes resulting from disease. Nevertheless, it is to be expected that newer and better drugs will be forthcoming, with greater selectivity of action and shorter duration of effect. With the development of such compounds, the clinical uses of drugs of this type can be more precisely defined and their dosages more accurately controlled and regulated. With improvements of this kind, the results of treatment with amine oxidase inhibitors should become increasingly satisfactory.

References

1. Selikoff, I. J., Robitzek, E. H. and Ornstein, G. G. Toxicity of hydrazine derivatives of isonicotinic acid in the chemotherapy of human tuberculosis (preliminary report). *Quart. Bull. Sea View Hosp.*, 13: 17, 1952.
2. Scherbel, A. L. Amine oxidase inhibitors; clinical experience in treatment of over 2000 cases. *J. Nerv. & Ment. Dis.*, in press.
3. Scherbel, A. L., Schuchter, S. L. and Harrison, J. W. A rational approach to the treatment of rheumatoid arthritis. v. Chemotherapy in rheumatoid arthritis: a concept. *Cleveland Clin. Quart.*, 24: 105, 1957.
4. Scherbel, A. L., McKittrick, R. L. and Hawk, W. A. The influence of serotonin and histamine on the growth of connective tissue in the rat. In preparation.
5. Scherbel, A. L., Curtis, G. H. and Harrison, J. W. The effect of iproniazid ointment on trophic ulcers associated with Raynaud's phenomenon; a clinical note. *Cleveland Clin. Quart.*, 25: 92, 1958.
6. Shore, P. A. and Brodie, B. B. LSD-like effects elicited by reserpine in rabbits pretreated with iproniazid. *Proc. Soc. Exper. Biol. & Med.*, 94: 433, 1957.
7. Scherbel, A. L., Harrison, J. W. and Atdjian, M. The treatment of rheumatoid arthritis complicated by chronic hypercortisonism, and the theoretical causal role of certain amine oxidases. *Cleveland Clin. Quart.*, 24: 219, 1957.
8. Keith, N. M., Wagener, H. P. and Barker, N. W.

Some different types of essential hypertension: their course and prognosis. *Am. J. M. Sc.*, 197: 332, 1939.

9. JOLLY, E. R. Iproniazid and angina pectoris (editorial). *Circulation*, 20: 1, 1959.
10. Personal communication. Hoffmann-La Roche, Inc., 1960.
11. SCHERBEL, A. L., HARRISON, J. W. and ATDJIAN, M. Further observations on the use of 4-aminoquinoline compounds in patients with rheumatoid arthritis or related diseases. *Cleveland Clin. Quart.*, 25: 95, 1958.
12. SCHERBEL, A. L. and HARRISON, J. W. The effects of iproniazid and other amine oxidase inhibitors in rheumatoid arthritis. *Ann. New York Acad. Sc.*, 80: 820, 1959.

Treatment of Angina Pectoris with a New Monoamine Oxidase Inhibitor, Pivalylbenzhydrazine*

ROBERT W. OBLATH, M.D. *and* GEORGE C. GRIFFITH, M.D., F.A.C.C.

Los Angeles, California

PIVALYLBENZHYDRAZINE (TERSAVID†) is a new, relatively non-toxic monoamine oxidase inhibitor which we have employed in the treatment of angina pectoris since June 1959. It is the purpose of this report to relate our experiences with this agent. We previously reported on the use of isocarboxazid (Marplan®)[1] in angina pectoris; the present paper includes a number of the patients who had been studied initially with that agent.

CASE MATERIAL AND METHODS

The group under study consisted of forty patients. Of these, eleven initially received isocarboxazid and later were transferred to pivalylbenzhydrazine; the remainder were given only the latter compound. The subjects all suffered from angina pectoris; the majority were seriously ill. Several patients with milder degrees of angina also were studied in order to observe the effects of these agents in those less seriously handicapped.

The underlying pathologic condition in thirty-four of the forty patients was coronary arteriosclerosis. In five, aortic stenosis was the significant lesion, and in one there was aortic insufficiency. In several, there was pre-existing myocardial infarction, two having occurred within the three months preceding treatment. In two, coronary insufficiency developed during treatment, in one just before. Of the forty patients, one has since died of coronary disease, one has been lost to follow-up, and the remainder are still under observation.

As was to be expected from the sex-age distribution of coronary artery disease, the majority of patients were male (twenty-four) and all were over the age of forty years, the range being from forty to seventy-nine years of age.

As the monoamine oxidase inhibitor was administered, all other so-called coronary dilators except nitroglycerin were discontinued. Several patients were on regimens directed toward possible modification of lipid metabolism. These types of treatment and all other supportive measures were continued in order to introduce as few variables as possible.

There is no separate control group in this series. Each of the patients had long been known to us or his own physician, either in private practice or at the Good Hope Clinic, and each had been treated for at least several months or even years with "standard" therapy before either isocarboxazid or pivalylbenzhydrazine was given. Each patient, therefore, served as his own control.

Clinical and Laboratory Studies: Effects of the medication were studied by evaluation of the degree of angina and the amount of nitroglycerin and other therapeutic agents used both before and after administration of the trial agent. Histories and physical examinations were carefully checked before and during treatment; capacity for effort was evaluated, and possible acute and chronic toxicity were studied by means of serial blood counts and urinalyses. Serially repeated serum glutamic oxaloacetic transaminase, prothrombin time, cephalin flocculation, alkaline phosphatase, serum bilirubin and urinary urobilinogen determinations were made in a number of patients. Studies are presently under way on the effects of the amine oxidase inhibitors, as exemplified by pivalylbenzhydrazine, on certain trace metals in blood.

Dosage: Administration of the agent was by one of two methods: (1) One was by starting at low doses, initially 25 mg. daily, but later in the study 50 mg. to 100 mg. daily, and then regulating each patient individually until either a desired result was obtained, or the preparation was stopped because of lack of effect or the appearance of undesired side

* From the Department of Medicine (Cardiology), School of Medicine, University of Southern California, Los Angeles, California.

† Pivalylbenzhydrazine (Ro 4-1634) was supplied through the courtesy of Robert J. Floody, M.D., Department of Clinical Investigation, Hoffmann-La Roche, Inc., Nutley, New Jersey.

effects. In this group, the dose was increased by increments of 25 mg. or 50 mg. daily at semiweekly, weekly or biweekly intervals. (2) The other technic was to start at a fixed dose level of 150 mg. or 200 mg. daily and maintain that dose. Twenty-one patients were treated in the former manner; nineteen in the latter.

Of the "individualized group," two were started at 25 mg., fifteen at 50 mg., one at 75 mg., and three at 100 mg. daily. It was found that the full therapeutic effect was obtained at 50 mg. in one, 75 mg. in three, 100 mg. in eight, 150 mg. in four and 200 mg. daily in one patient. In one patient the dose was started at 75 mg. daily, dropped to 50 mg. per day and then stopped because insomnia of severe degree developed. Another patient was started at 50 mg. a day, increased to 75 mg. and achieved benefit, but then stopped the medication because he became "jittery." He was found later to be a user of large amounts of alcoholic beverages. One patient had been gradually increased to a dose of 300 mg. daily; his angina, which had improved, then became worse and at his request he was again given isocarboxazid, which he had previously taken, with good results. Where he had required 30 mg. of isocarboxazid previously, he now requires 40 mg. per day for equal benefit. One other patient had a somewhat similar experience at 100 mg. per day, refused to take more, and was again given isocarboxazid. This patient had previously required 10 mg. for good results; after being restarted on isocarboxazid, she achieved equal benefit with only 5 mg. per day for three months, then found it necessary to take more and has felt well with 10 mg. daily for the past eight weeks.

Of those patients, then, who have achieved good results by the first method of administration, the average dose appears to be a little over 100 mg. per day. No such estimation of average dose is possible in the other group because of the fixed method of administration employed.

Results

Results were evaluated by means noted earlier. As far as frequency and severity of angina and the amount of nitroglycerin used is concerned, results were considered excellent if each of these decreased an estimated 75 per cent or more, good or fair if between 25 and 75 per cent and no effect if less than 25 per cent. Similarly, improvement in capacity for effort was estimated and appeared to agree with the other factors noted.

Nineteen patients (47.5 per cent) achieved excellent results, fourteen (35 per cent) were considered good, and four (10 per cent) appeared to obtain no effect. Three (7.5 per cent) felt they were made worse, not from the standpoint of angina, but from that of increased tension and jitteriness. Eighty-two and a half per cent of our patients, therefore, appeared to have beneficial effects. This evaluation agrees fairly closely with our results with isocarboxazid.[1]

Two of the patients considered to have had good results later noted exacerbations of angina. They had initially received isocarboxazid and requested that it be given them again. This was done and improvement resulted as noted earlier. Conversely, one patient who could not tolerate isocarboxazid in even 5 mg. daily doses is now taking 200 mg. of pivalylbenzhydrazine daily with fair benefit. One other patient, in whom severe postural hypotension developed (although angina was relieved almost completely) with 10 mg. of isocarboxazid daily for six weeks, has now taken pivalylbenzhydrazine for four months with complete relief of angina and without side effects. This patient was started with 25 mg. daily which was gradually increased to 75 mg. per day. Her dose requirement seems to be equally low for both drugs.

Pivalylbenzhydrazine does not appear to differ from either iproniazid or isocarboxazid in the length of time required to obtain therapeutic effect. Eleven patients were given first isocarboxazid and later pivalylbenzhydrazine. In several cases, as the newer agent replaced the older, the newer was given in such small doses that the amine oxidase inhibiting effect of the older was allowed to wear off. The dose of the newer one was then increased until an adequate amount was given. In each instance, the time from initiation of the proper dose until an effect was obtained was roughly the same with each preparation, varying from twenty-four hours in one patient, an average of four to seven days for the majority, to an upper extreme of about one month. One patient was treated for almost two months before his capacity for effort definitely improved and benefit persisted. In these patients, and in those whose angina recurred when the inhibitor was withdrawn, the time interval from dose change to renewal or exacerbation of symptoms roughly paralleled the time initially required to obtain effect. In several patients, the medication was discontinued to see if the beneficial effect was permanent; it was in only one patient.

Side Effects: At the time of writing, patients have been treated with pivalylbenzhydrazine for from one to ten months. No significant changes have been found on physical examination, in blood pressure or in weight. No serious side ef-

fects have been noted. Several patients have complained of insomnia, jitteriness and increased tension. One patient noted a sensation of epigastric fullness; another, slight tenesmus and loose stools. The most serious side effect has been urticaria and pruritus, which appeared in one patient within forty-eight hours of changing from isocarboxazid to pivalylbenzhydrazine. This complication subsided in forty-eight hours and has not recurred despite the fact that the patient continued to take the medication. Of great importance, we believe, is the fact that orthostatic hypotension has not developed in any of our patients while taking pivalylbenzhydrazine. One patient died after eight months of therapy with isocarboxazid followed by two months' therapy with pivalylbenzhydrazine. Nothing was observed at necropsy which could be related in any way to the use of these agents.

Toxic Effects: No unusual variations were observed in blood counts and urinalyses, performed serially in all patients. Urinary urobilinogen, serum glutamic oxaloacetic transaminase, alkaline phosphatase, total bilirubin, cephalin flocculation and prothrombin time determinations were made serially in thirteen patients. The initial determinations were not made in several until they had taken the medications for many months. In no instance has any serious abnormality appeared. Five have had fluctuations in the cephalin flocculation, the test going as high as 3 plus in forty-eight hours in one patient, later reverting to normal. Two patients have had minor elevations in the direct one-minute serum bilirubin. The alkaline phosphatase was minimally elevated on three occasions. In none of these patients was treatment stopped, nor did any serious complication ensue. The abnormal tests later reverted to normal in each instance while use of medication continued. Blood cholesterol determinations and lipoprotein fractionations by paper electrophoresis were made in four patients with no change appearing which could be ascribed to the medications used. Resting electrocardiograms showed no consistent changes which could be distinguished from those occurring due to coronary disease and its variations.

Trace Metal Determinations: Such determinations* have been made in serum samples taken from five patients. At present, data are inconclusive; only preliminary observations may be noted. The five patients had received monoamine oxidase inhibitors for at least two months. Three of the five previously had been given isocarboxazid—one had been given it again for two months before blood was drawn for these tests. Results in this patient were similar to those observed in patients given pivalylbenzhydrazine.

We found serum manganese and copper elevated in four of five patients and normal in one; the value for aluminum was borderline in one, high in two and normal in two; serum zinc, lead and iron were normal in all five. None of the associated laboratory tests noted previously was abnormal in any of these patients, particularly the serum glutamic oxaloacetic transaminase, which Hegde and others[2] have found correlated with elevation of serum manganese in the acute stage of myocardial infarction. The significance of these variations is not known; conjecture would be idle at this point. A long-term study is now being made and will be the subject of a detailed report in the future.

Comments

A comparison of pivalylbenzhydrazine with isocarboxazid indicates that these agents are generally comparable as regards their relief of angina pectoris. Pivalylbenzhydrazine, however, is not as potent an analeptic agent as is isocarboxazid. At least three of the patients who were transferred from the latter to the former commented that while they achieved as much relief of their pain by means of pivalylbenzhydrazine, they did not "feel as well" as when they were taking isocarboxazid. Depressed patients seemed to respond better to isocarboxazid.

Because our series is small, we are unable to approximate equivalent doses of these medications. In those who used both sequentially, however, we found 20 to 30 mg. of isocarboxazid apparently as effective in the treatment of angina pectoris as 100 to 200 mg. of pivalylbenzhydrazine.

We have noted that many physicians deny their patients the use of the monoamine oxidase inhibitors because of fear of hepatic toxicity. Our patients have been followed up carefully; in none of them has this complication appeared. In our experience this is sufficiently rare so as not to justify denial of the benefits of these agents to these crippled and unhappy patients.

We have noted also that many physicians fear these agents because, with pain masked, there is the possibility that the patients will overdo, and

* These determinations were obtained with the cooperation of Dr. Edward M. Butt and Dr. Balakrishna Hegde.

silent myocardial infarctions or heart failure will develop. We are not at all sure that the relief of pain is a simple masking. Furthermore, while excellent relief of pain is achieved, it has been noted consistently that if these patients go too far in their activities, as a rule, symptoms develop sufficiently early to be brought under adequate control. Much, of course, depends upon the cooperativeness of the individual patient. In only one of our total group did we have any real problem, and this particular patient has since learned her restrictions and stayed within them. At the same time, other patients, previously disabled, are once again leading relatively normal lives, being gainfully employed and self-sufficient.

Summary

Pivalylbenzhydrazine was administered to forty patients over a period ranging from one to ten months in maintenance doses of 50 to 300 mg. per day. The majority required 100 to 200 mg. daily for therapeutic effect. Excellent results were obtained in nineteen (47.5 per cent), good or fair results in fourteen (35 per cent), and no effects in four (10 per cent). This is similar to the results obtained with isocarboxazid, though the latter appeared to be a better analeptic agent. No serious side effects or toxicities have been noted clinically or in the laboratory, particularly as related to orthostatic hypotension or hepatitis, neither of which was observed.

A study of the effects of monoamine oxidase inhibitors on trace metals in humans is now being made. Preliminary results indicate elevation of serum manganese, copper and aluminum, but no effect on zinc, lead and iron.

We have found pivalylbenzhydrazine to be an effective and apparently safe agent in the treatment of angina pectoris.

References

1. Oblath, R. W. Paper read at American Therapeutic Society, 60th Annual Meeting, Atlantic City, New Jersey, June 6, 1959.
2. Hegde, B., Griffith, G. C. and Butt, E. M. Serum manganese concentration as a measure of myocardial damage; comparison with SGOT levels. Paper read at Regional Meeting of the American College of Physicians, Coronado, California, February 7, 1960.

The Use of Monoamine Oxidase Inhibitors as Adjuncts in the Treatment of Hypertension and Angina Pectoris*

WILLIAM HOLLANDER, M.D., ARAM V. CHOBANIAN, M.D. *and* ROBERT W. WILKINS, M.D.

Boston, Massachusetts

CORONARY ARTERY disease is one of the major complications of arterial hypertension. Although its apparent progress may be retarded by effective lowering of the blood pressure with antihypertensive drugs, there is no convincing evidence that the disease in its advanced stages is reversible by a simple lowering of the blood pressure. Therefore, an intensive search has been undertaken not only for more effective antihypertensive drugs but also for agents which might have a direct beneficial effect on the vascular complications of arterial hypertension.

After Cesarman[1] and Cossio[2] had reported that iproniazid had an antianginal effect, it was decided to study this compound and other monoamine oxidase inhibitors in arterial hypertension, especially since we had been interested in drugs such as rauwolfia and BAS (benzyl analogue of serotonin)[3–5] which also alter the metabolism of serotonin and norepinephrine.[6,7] The present study, which began a little over two years ago,[8] reviews our experience with iproniazid and some of the newer amine oxidase inhibitors in arterial hypertension and angina pectoris.

The chemical structures of some of the tested amine oxidase inhibitors are shown in Figure 1. The compounds contain a hydrazine group which appears to be mainly responsible for their activity. The clinical actions of these agents are similar and include an antidepressive, antianginal and antihypertensive effect. Although there is abundant proof that the hydrazine derivatives are potent inhibitors of amine oxidase, it has not been clearly established that all their clinical actions result from an inhibition of monoamine oxidase. It is noteworthy that hydralazine (Apresoline®), which is effective as an antihypertensive agent but which aggravates angina pectoris, is a hydrazine derivative that does not inhibit monoamine oxidase *in vivo*.[9]

HYPERTENSION

Hypertension Associated with Angina Pectoris: The effects of iproniazid in one of our first patients treated with an amine oxidase inhibitor are shown in Figure 2. The patient had continued to have hypertension and frequent attacks of angina pectoris even though she had previously undergone splanchnicectomy and was receiving rauwolfia. Following the institution of iproniazid in a daily dosage of only 50 mg. the patient became more anxious and irritable, but nevertheless had striking reductions in blood pressure and in the number of attacks of angina pectoris without a change in the electrocardiographic pattern of left ventricular hypertrophy. During continued iproniazid therapy there also was a slight decrease in serum cholesterol without a significant change in serum transaminase values. These findings were encouraging but did not clearly establish that the concomitant reductions in angina attacks and in serum cholesterol were due to a direct action of iproniazid since such changes may also occur following a reduction in blood pressure by other antihypertensive agents. However, they did indicate that the relief of angina pectoris following iproniazid therapy may occur without a clinical improvement in the psychological state of the patient.

The effects of different amine oxidase in-

* From the Department of Clinical Research and Preventive Medicine, Massachusetts Memorial Hospitals, Boston, Massachusetts.

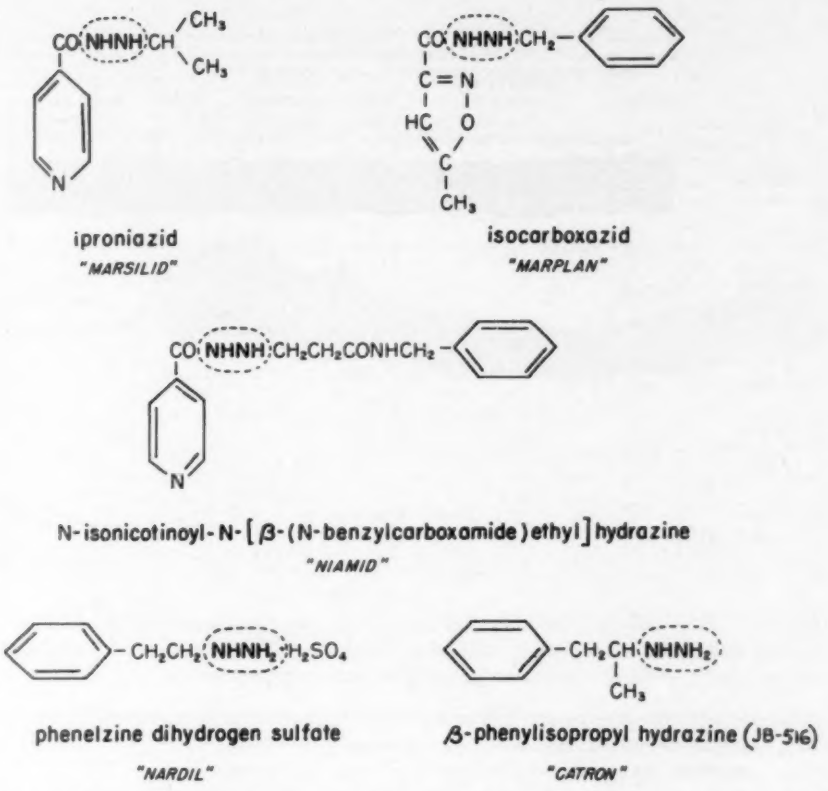


FIG. 1. Amine oxidase inhibitors of the hydrazine class. Chart comparing the chemical structures of some of the monoamine oxidase inhibitors. The hydrazine groups of these compounds are circled with broken lines.

hibitors in a subject with severe hypertension and angina pectoris are illustrated in Figure 3. The patient's condition had failed to respond satisfactorily to reserpine and hydrochlorothiazide. When either iproniazid, pheniprazine (Catron®) or isocarboxazid (Marplan®) was added to the treatment, the blood pressure remained essentially at its pre-existing high level, but the anginal attacks gradually decreased in frequency and finally disappeared after three weeks of therapy. As the angina improved, the patient developed a feeling of well-being, and was able to increase his activities and return to full time work. It is noteworthy that the electrocardiograms following repeated two-step exercise tolerance tests continued to show the same changes consistent with coronary insufficiency even when the anginal attacks had been abolished by the amine oxidase inhibitors. The serum cholesterol and transaminase levels also did not change significantly with treatment. These and parallel studies indicate that the antianginal and antihypertensive effects of amine oxidase inhibitors may be independent actions of these compounds. They also suggest further that changes in serum cholesterol during treatment are related to the changes in blood pressure.

Resistant Hypertension: The blood pressure responses to iproniazid, pheniprazine and isocarboxazid in a resistant case of hypertension are shown in Figure 4. The blood pressure remained at hypertensive levels even though the subject was receiving pentolinium,

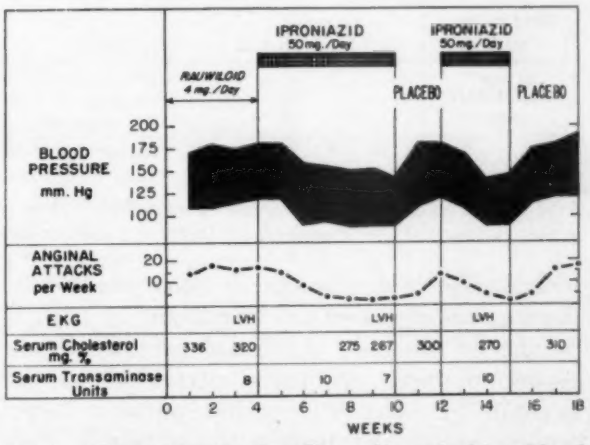


FIG. 2. Chart showing the effects of iproniazid on blood pressure, anginal attacks, EKG and serum cholesterol and transaminase levels in a splanchnicectomized hypertensive subject with angina pectoris.

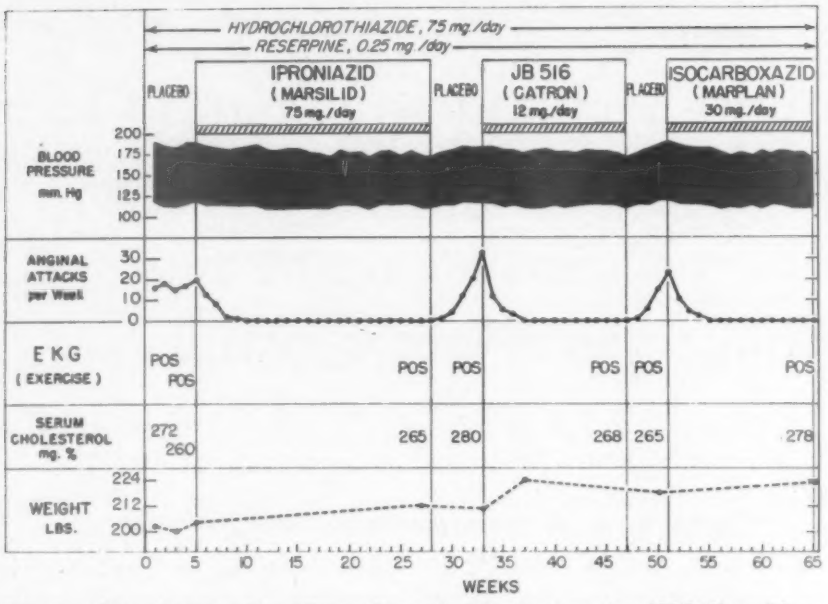


FIG. 3. Chart showing the effects of iproniazid, pheniprazine (JB516) and isocarboxazid on blood pressure, anginal attacks, EKG and serum cholesterol and transaminase levels in a hypertensive subject with angina pectoris.

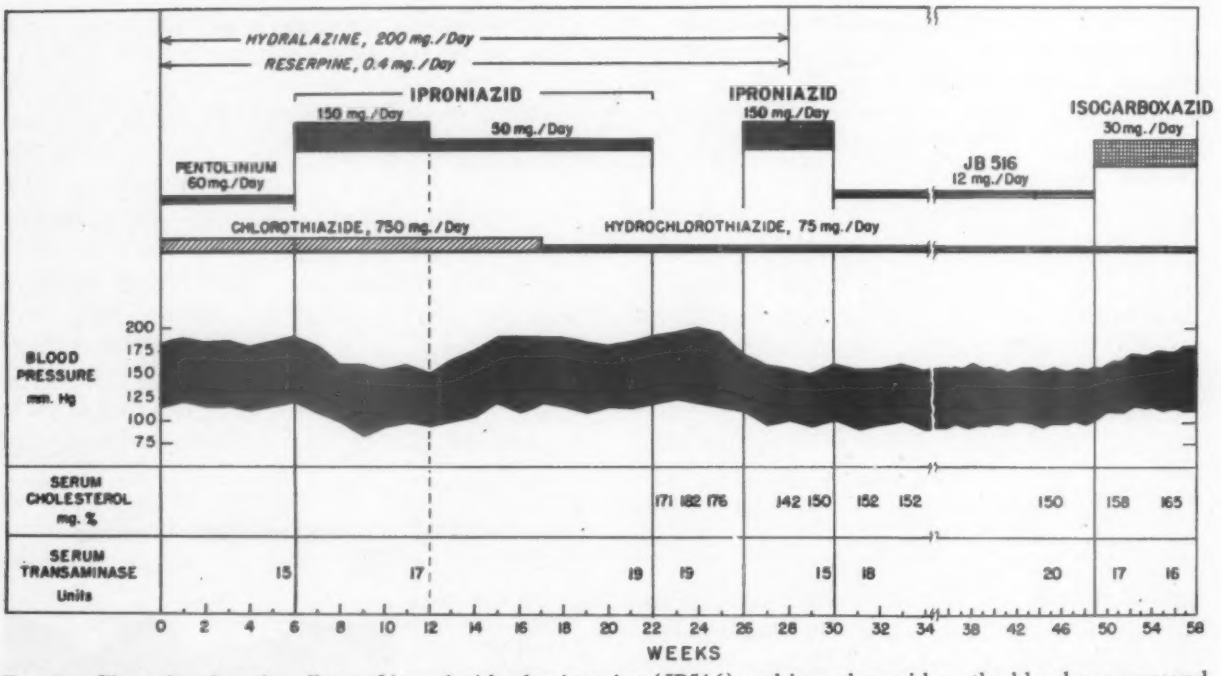


FIG. 4. Chart showing the effects of iproniazid, pheniprazine (JB516) and isocarboxazid on the blood pressure and serum cholesterol and transaminase levels in a subject with essential hypertension.

hydralazine and reserpine. After the pentolinium was replaced by iproniazid in a daily dosage of 150 mg., the blood pressure in the sitting position gradually decreased toward normal. During this period postural hypotension as well as dryness of the mouth, constipation and urinary difficulty developed—side effects resembling those produced by ganglionic blocking agents. After the dosage of iproniazid was reduced, these side effects as well as the hypotensive action of iproniazid disappeared. When pheniprazine was substituted for iproniazid later in the study, the reduction in blood pressure was maintained without side effects except for orthostatic hypotension. However, the blood pressure rose after pheniprazine was replaced by isocarboxazid. The serum transaminase levels remained normal during treat-

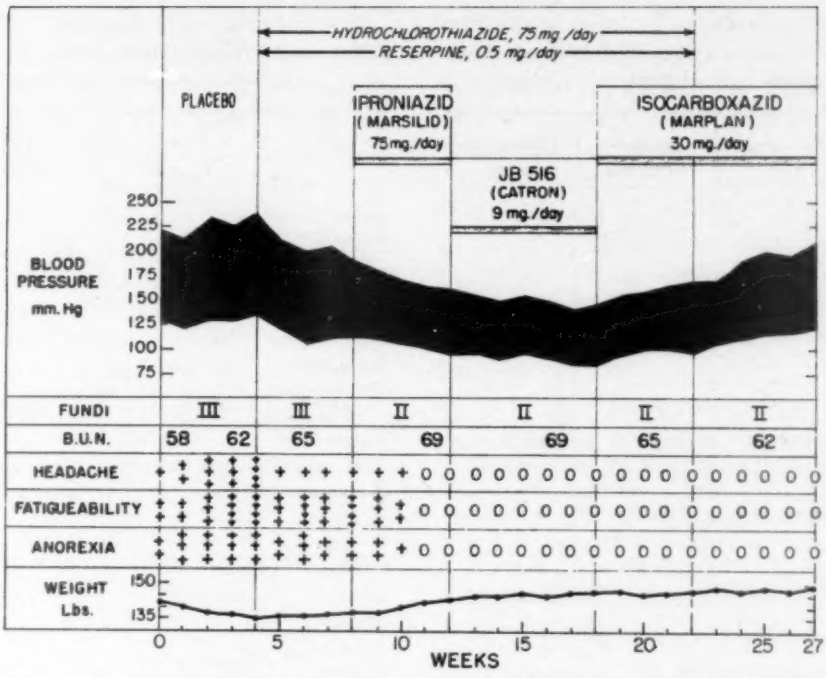


FIG. 5. Chart showing the effects of iproniazid, pheniprazine (JB516) and isocarboxazid in a hypertensive subject with complicating renal insufficiency.

ment, whereas serum cholesterol decreased slightly in association with lowering of the blood pressure.

Hypertension and Renal Insufficiency: The effects of the amine oxidase inhibitors in a hypertensive patient with complicating renal insufficiency are shown in Figure 5. In the control period the patient complained of occipital headaches, weakness and loss of appetite which was associated with severe hypertension, grade III retinopathy and nitrogen retention. After the administration of hydrochlorothiazide and reserpine there was a moderate decrease in blood pressure and in the frequency of headache without an appreciable change in the blood urea nitrogen or the symptoms of renal insufficiency.

After iproniazid or pheniprazine was added to the therapy there was a further reduction in blood pressure which was followed by a disappearance of headache and retinal exudate. Although the blood urea nitrogen remained elevated, the patient experienced a feeling of well-being and an increase in appetite and weight. When isocarboxazid was substituted for pheniprazine the blood pressure rose somewhat but the patient continued to be relatively asymptomatic. These observations indicate that the amine oxidase inhibitors are capable of producing marked clinical improvement in the psychological state without necessarily affecting the underlying disease process.

Side Effects: As shown in Table 1, the side

TABLE 1
Side Effects of Amine Oxidase Inhibitors in Twenty-Five Cases

Side Effects	Iproniazid (Marsilid)	Isocarboxazid (Marplan)	β-Phenylisopropyl hydrazine (JB-516) (Catron)
Blurring of vision	2	2	3
Dryness of mouth	7	3	3
Constipation	7	3	3
Urinary difficulty	2	1	1
Orthostatic dizziness	2	1	2
Orthostatic syncope	1	0	1
Orthostatic angina	1	0	1
Headache	2	0	0
Neuralgia	2	0	0
Paresthesia	3	1	1
Reduced libido	4	3	3
Anxiety	2	1	2
Irritability	2	2	3
Insomnia	4	2	3
Epigastric distress	4	1	1
Weight gain	4	4	4
Jaundice	0	0	0
Elevated serum transaminase	0	0	0

TABLE II

Effect on Blood Pressure of Three Amine Oxidase Inhibitors* in Twenty-Five Hypertensive Subjects

	Iproniazid	Isocarboxazid	Pheniprazine
Response rate	52%	32%	72%
Average blood pressure reduction (mm. Hg)	18/10	10/6	24/15
Range of blood pressure reduction (mm. Hg)	15/10–55/25	15/10–55/25	15/10–75/30
Average dosage (mg./day)	50	20	9
Dosage range (mg./day)	25–75	10–30	3–18

* Added to other antihypertensive drugs.

TABLE III

Effect on Angina of Three Amine Oxidase Inhibitors in Eighteen Subjects with Angina Pectoris

	Iproniazid	Isocarboxazid	Pheniprazine
Response rate	50%	56%	56%
Average reduction in angina	48%	54%	58%
Range of reduction in angina	25–100%	25–100%	25–100%
Electrocardiogram	Unchanged	Unchanged	Unchanged
Average dosage (mg./day)	50	20	9
Dosage range (mg./day)	25–75	10–30	3–18

effects of the various amine oxidase inhibitors were similar but occurred less frequently with the newer agents than with the older iproniazid. The occurrence of blurring of vision, dryness of the mouth, constipation, urinary difficulties and orthostatic hypotension suggest that the amine oxidase inhibitors also have a ganglionic blocking action. Although some of these compounds, especially iproniazid, have been reported to cause severe liver disease in rare instances, no impairment of liver function, as indicated by the appearance of jaundice or an elevated serum transaminase, was detected in this small series of cases.

Comparative Antihypertensive Effects of Various MAO Inhibitors: The comparative effects of iproniazid, isocarboxazid and pheniprazine on the blood pressure of twenty-five hypertensive subjects are summarized in Table II. The tabulated blood pressure responses are those which occurred following the addition of these compounds to other antihypertensive drugs which included rauwolfia, hydralazine, chlorothiazide or ganglionic blockers. When used alone, the various amine oxidase inhibitors usually had no marked effect on the blood pressure. However, as shown in Table II, they were moderately effective as antihypertensive agents when combined with other drugs, especially chlorothiazide and its analogs. Of the amine oxidase inhibitors, which included phenelzine and nialamide, pheniprazine exhibited the greatest antihypertensive activity. Recent observations with a newer amine oxidase inhibitor, DL-serine-N^2-isopropylhydrazide, support those data previously reported by Maxwell and co-workers[10] and indicate that this compound in combination with other drugs also is an effective and useful antihypertensive agent.

The hypotensive action of the amine oxidase inhibitors, which frequently included an additional postural hypotensive effect, usually began within four to eight days and was maximal within two to three weeks after starting treatment; when the compounds were withdrawn, their hypotensive effects persisted for about one week but lasted in some cases as long as two to three weeks.

ANGINA PECTORIS

Table III summarizes the effects of some of the amine oxidase inhibitors on angina pectoris. When added to other antianginal or antihypertensive regimens, these agents appeared to produce a considerable reduction in anginal attacks in about 50 per cent of the cases. The antianginal effects of the amine oxidase inhibitors appeared to be comparable and were inconsistently related to the concomitant changes in blood pressure. Excellent results were obtained in three subjects who had a complete cessation of angina while receiving these agents. A limited experience with

phenelzine and nialamide also indicates that these amine oxidase inhibitors have antianginal actions. With the improvement in angina pectoris most of the patients experienced a sense of well-being and led a more active, normal life. The relief of angina occurred three to twelve days after administration of the drug was begun and persisted after withdrawal of the drug for three to twenty-eight days.

Even though the amine oxidase inhibitors produced a remarkable improvement in angina in some cases, they did not alter significantly the resting electrocardiograms. They likewise had no appreciable effect on the electrocardiogram following the two-step exercise tolerance test in six subjects, all of whom continued to show electrocardiographic signs of myocardial ischemia on treatment. These findings suggest that the antianginal effect might be due to an interference with the transmission or conscious appreciation of pain impulses from the heart and not necessarily to an improvement in the adequacy of the coronary circulation. Although a removal of the pain signal of coronary insufficiency might aggravate the basic disease process, the incidence of myocardial infarction in this small series of patients who received amine oxidase inhibitors continuously for three to twelve months was low. The one patient who had this complication had a poor symptomatic response to treatment. In view of these observations, additional longer term studies are necessary if it is desired to establish the mode of action of the amine oxidase inhibitors in angina pectoris.

Summary

The newer monoamine oxidase inhibitors have clinical actions in hypertension and angina pectoris similar to those of iproniazid but appear to produce less frequent side effects. Some of the side effects suggest that in addition to amine oxidase inhibition, they may also have a ganglionic blocking action.

The amine oxidase inhibitors are effective and useful in the clinical management of refractory cases of angina pectoris even though they may not alter the electrocardiogram significantly. Since the relief of chest pain also is accompanied frequently by a sense of well-being, cautioning the patient against overexertion is advisable. Some of the amine oxidase inhibitors are also worthy of a trial in resistant cases of hypertension. However, they should be employed cautiously in these selected cases since their long term effects, even in moderate dosage, on liver and cardiac function are not known.

References

1. Cesarman, T. Serendipity and angina pectoris. Preliminary report on a therapeutic discovery. *Arch. Inst. cardiol. México*, 27: 563, 1957.
2. Cossio, P. The treatment of angina pectoris and other muscular pain with iproniazid phosphate. *Prensa méd. argent.*, 44: 2679, 1957.
3. Wilkins, R. W. and Judson, W. E. The use of rauwolfia serpentina in hypertensive patients. *New England J. Med.*, 248: 48, 1953.
4. Hollander, W., Michelson, A. L. and Wilkins, R. W. Serotonin and antiserotonins. I. Their circulatory, respiratory and renal effects in man. *Circulation*, 16: 246, 1957.
5. Wilkins, R. W. and Hollander, W. Serotonin and antiserotonins. II. Clinical studies, especially in essential hypertension with the benzyl analog of serotonin (BAS). *Circulation*, 16: 256, 1957.
6. Shore, P. A., Mead, J. A. R., Knutzman, R. G., Spector, S. and Brodie, B. B. On the physiologic significance of monoamine oxidase in brain. *Science*, 126: 1063, 1957.
7. Udenfriend, S., Weissbach, H. and Bogdanski, D. F. Biochemical findings relating to the action of serotonin. *Ann. New York Acad. Sc.*, 66: 602, 1957.
8. Hollander, W. and Wilkins, R. W. Iproniazid and other amine oxidase inhibitors in arterial hypertension with or without complicating angina pectoris. In: Hypertension: The First Hahnemann Symposium on Hypertensive Disease, p. 399. Edited by J. H. Moyer. Philadelphia, 1959. W. B. Saunders Co.
9. Sjoerdsma, A. Monoamine oxidase inhibitors. In: Hypertension: The First Hahnemann Symposium on Hypertensive Disease, p. 186. Edited by J. H. Moyer. Philadelphia, 1959. W. B. Saunders Co.
10. Maxwell, M. H., Roth, S. I., Pearce, M. L. and Kleeman, C. R. Hypotensive properties of a new monoamine oxidase inhibitor: DL-serine-N^2-isopropylhydrazide. Proceedings of the 32nd Scientific Sessions, American Heart Association, p. 738, 1959.

Nialamide in the Treatment of Essential Hypertension*

ALBERT N. BREST, M.D., CRISTOBAL DUARTE, M.D. *and* JOHN H. MOYER, M.D., F.A.C.C.
Philadelphia, Pennsylvania

IPRONIAZID (MARSILID®) was the first monoamine oxidase (MAO) inhibitor to be used clinically, initially as a tuberculostatic drug and later as a psychic energizer and antianginal agent. Several investigators also reported the drug to be useful in the treatment of hypertension, and subsequently other MAO inhibitors were found to have significant hypotensive abilities.[1-4] The clinical usefulness of these compounds has been limited, however, by the development of severe toxic reactions including hepatic cellular damage and loss of color discrimination.[4,5] It is the purpose of this report to discuss the MAO inhibitor, nialamide, which appears to have a high index of safety in addition to significant antihypertensive effectiveness.

METHODS AND MATERIALS

Twenty-five ambulatory patients with a blood pressure greater than 150/100 mm. Hg were randomly selected from the Hypertension Clinic. After an initial diagnostic evaluation, these subjects were given daily placebo medication for a minimum period of at least three weeks. The patients returned to the clinic at weekly intervals, at which time blood pressure and physical signs and symptoms were recorded. After the control period, nialamide† was begun in a dosage of 75 mg. daily (25 mg. three times a day). Thereafter the dosage was increased at biweekly intervals, to a maximum of 225 mg. daily (75 mg. three times a day) unless a significant hypotensive response‡ was achieved at a lower dosage.

The initial clinical trial with nialamide (as the sole antihypertensive agent) was limited to an eight-week period. Thereafter, hydrochlorothiazide§ was added to the antihypertensive regimen in those subjects in whom a significant hypotensive response had not been achieved. The initial dosage of hydrochlorothiazide was 50 mg. daily (25 mg. twice a day). After two weeks the dosage was increased to 100 mg. per day (50 mg. twice a day) if a significant reduction of blood pressure had not been obtained. The combination of nialamide (75 mg. twice a day) and hydrochlorothiazide was administered for a minimum period of at least eight weeks. Serum sodium and potassium, blood urea nitrogen and cephalin flocculation were measured during the control period and at the end of the study.

† Supplied as Niamid® by Chas. Pfizer Co., Inc., New York, New York.

‡ A reduction in mean arterial blood pressure (diastolic pressure plus one-third of the pulse pressure) of 20 mm. Hg or more was considered significant.

§ Supplied as Hydrodiuril® by Merck, Sharp & Dohme, West Point, Pennsylvania.

RESULTS

Nialamide Given Alone: The blood pressure response is tabulated in Table I. Of the twenty-five patients in this group, five (20 per cent) obtained a drop in mean arterial blood pressure of more than 20 mm. Hg in the supine position. When blood pressure was recorded in the upright position, eleven patients (44 per cent) obtained a significant hypotensive response, and seven of the eleven became normotensive.

The side effects and beneficial effects are listed in Tables II and III, respectively. No serious reactions were encountered. Drowsiness, orthostatic weakness, dreams and anxiety were the most prominent complaints but were seen in only a few patients.

Nialamide Plus Hydrochlorothiazide: The blood pressure response is tabulated in Table I. Among the seventeen patients who received combined therapy with nialamide and hydrochlorothiazide, only three (18 per cent) obtained a reduction in mean arterial blood pressure of more than 20 mm. Hg in the supine position. However, when the blood pressure was recorded in the upright position, eleven subjects (65 per cent) obtained a significant hypotensive response, and seven of the eleven became normo-

* From the Hypertension Unit, Department of Internal Medicine, Hahnemann Medical College and Hospital, Philadelphia, Pennsylvania.

TABLE I
Blood Pressure Response to Nialamide Given Alone and in Combination with Hydrochlorothiazide

Drug	No. of Patients	Supine Position			Upright Position		
		Normotensive*	Mean Blood Pressure Reduced >20 mm. Hg or Normotensive	Unresponsive	Normotensive*	Mean Blood Pressure Reduced >20 mm. Hg or Normotensive	Unresponsive
Nialamide	25	5	5	20	7	11	14
Nialamide plus hydrochlorothiazide	17	3	3	14	7	11	6

* Blood pressure reduced to 150/90 mm. Hg or less.

tensive. A typical response is illustrated in Figure 1.

The side effects and beneficial effects are listed in Tables II and III, respectively. The most prominent side effect encountered was drowsiness, which occurred in seven patients. Less common complaints were orthostatic weakness, constipation and dreams.

Serum Electrolytes and Chemical Studies: Significant changes in the serum electrolytes (sodium or potassium) did not occur with either antihypertensive regimen. Although one patient had a serum sodium of 130 mEq./L. (after combined nialamide-hydrochlorothiazide therapy) and an additional subject had a serum potassium of 3.0 mEq./L. (also after combined treatment), there were no instances of clinical electrolyte imbalance. The blood urea nitrogen rose to 27 mg. per cent in one patient on the combined regimen (the control value in this subject was 19 mg. per cent), but no other significant changes in the blood urea nitrogen were noted. The cephalin flocculation increased to 3-plus in two patients who received nialamide for a period of sixteen

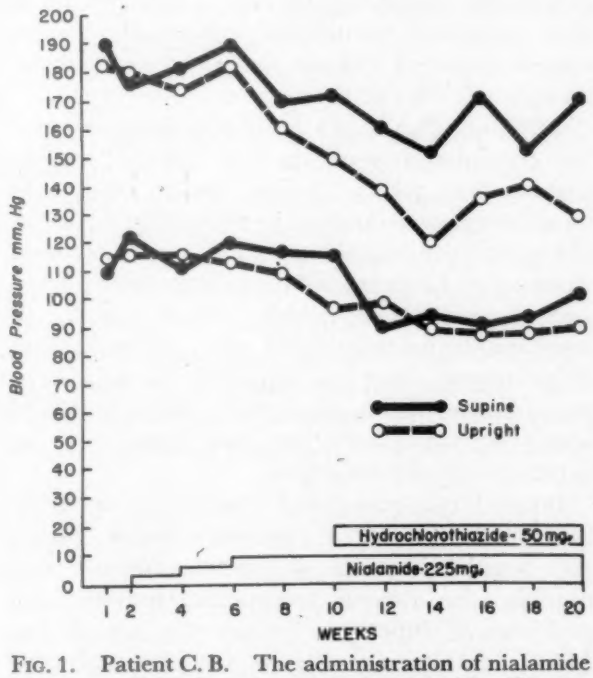


FIG. 1. Patient C. B. The administration of nialamide (225 mg. T.I.D.) and hydrochlorothiazide (50 mg. B.I.D.) resulted in a reduction of the upright blood pressure to normotensive levels; however, the supine pressure remained elevated.

TABLE II
Side Effects in Patients Treated

Side Effect	Nialamide Alone (%)	Nialamide Plus Hydrochlorothiazide (%)
Headache	8	6
Dry mouth	8	..
Nasal congestion	8	6
Edema	8	6
Increased appetite	12	12
Nausea	4	6
Constipation	8	24
Orthostatic weakness	25	24
Drowsiness	28	41
Depression	8	12
Dreams	20	24
Anxiety	20	6

TABLE III
Beneficial Effects on Symptoms

Symptom	Nialamide Alone		Nialamide Plus Hydrochlorothiazide	
	No. of Patients Who Complained before Therapy	No. of Patients Improved	No. of Patients Who Complained before Therapy	No. of Patients Improved
Headache	9	3	6	4
Chest pain	...	...	...	...
Dyspnea	6	3	5	2
Edema	2	1	1	1
Nausea	1	1	1	1
Constipation	2	1	1	1
Dizziness	10	3	8	3
Depression	1	1	1	1
Anxiety	3	2	2	1

weeks; however, in all other instances the cephalin flocculation remained within normal limits.

COMMENTS

Monoamine oxidase (MAO) is an enzyme which actively destroys various monoamines including norepinephrine, epinephrine and serotonin. It would therefore be anticipated that the MAO inhibitors would cause an accumulation of these hormones in muscle and nerve tissues, where they normally account for smooth muscle contraction and neurogenic transmission. Hence it seems rather paradoxic that hypotension should occur since the anticipated result would be a hypertensive response secondary to the increased concentration of these pressor substances. It is of interest in this regard that certain patients with norepinephrine-producing tumors (pheochromocytoma) may have a supine elevation of blood pressure but a marked postural hypotensive effect; similarly, hypotensive episodes may also occur in patients with hyperserotonemia due to malignant carcinoid tumors.

Any statement concerning the mechanism by which the MAO inhibitors lower blood pressure is entirely speculative at this time; however, some insight into the hypotensive abilities of these compounds may be obtained from a review of their clinical actions. The hypotensive response is mainly a postural one and the side effects which have been reported with certain of the MAO inhibitors, e.g., iproniazid, are similar to those encountered with the ganglion blocking agents.[3] These have included blurring of vision, dryness of the mouth, constipation and urinary difficulty. The combination of these two clinical findings has therefore suggested that the antihypertensive effectiveness of the MAO inhibitors may be due to ganglionic blockade. It is noteworthy, however, that the incidence of parasympatholytic side effects was not particularly high in the present study with nialamide; some of the other MAO inhibitors, including JB-516 (Catron®), have also produced significant orthostatic hypotensive responses without associated parasympatholytic side effects.[4]

Although the MAO inhibitors may increase the concentration of various biologic amines within the bodily tissues (brain, heart),[6,7] these compounds appear to exert little effect on the peripheral metabolism of these substances. Friend et al.[8] determined the plasma epinephrine and norepinephrine levels during infusion of norepinephrine before and after administration of iproniazid. Not only was there no significant potentiation of the physiologic effects or blood levels by iproniazid but also there was no prolongation of these effects.

Brodie[9] has postulated that norepinephrine and serotonin act as neurohormones within the central nervous system to control and regulate the various autonomic, somatic and psychogenic functions. Since the use of the MAO inhibitors results in an increased concentration of these substances within the brain tissue, it is conceivable that the hypotensive abilities of these compounds may be intimately

involved with this particular effect. However, much more investigative work needs to be accomplished in this regard.

The clinical findings obtained with nialamide indicate that this drug, like the other MAO inhibitors, is capable of effectively reducing blood pressure when used in relatively high dosage (225 mg. daily). However, this compound is considerably more effective when used in combination with hydrochlorothiazide, and the hypotensive effect obtained with this agent (whether used alone and/or in combination) is most pronounced in the upright position (Fig. 1). Although no attempt was made to increase the dosage of nialamide above 225 mg. daily, it is conceivable that the administration of larger oral doses might result in an even greater antihypertensive response. The incidence of side effects encountered was low; although the cephalin flocculation increased to 3-plus in two patients, there were no instances of clinical hepatotoxicity.

Further study of the clinical usefulness of the MAO inhibitors in essential hypertension is warranted and may ultimately provide a clue to the pathogenesis of this important disease process. Finally, because of the additional beneficial effects of these compounds in the treatment of angina pectoris, it may well be that these drugs will be particularly indicated in the hypertensive subject with complicating coronary artery disease.

Summary

The antihypertensive effectiveness of the monoamine oxidase (MAO) inhibitor, nialamide, was investigated. When nialamide was administered in relatively high dosage (225 mg. daily), 44 per cent of the subjects obtained a significant postural reduction of blood pressure; however, when the drug was used in combination with hydrochlorothiazide, 65 per cent of the group had a significant fall of blood pressure. In the supine position, a significant reduction of blood pressure was noted less often, in 20 and 18 per cent of the two groups, respectively. The incidence of side effects encountered was low and there were no instances of clinical hepatotoxicity.

The mechanism of hypotensive action of the MAO inhibitors is still undetermined. The various speculative mechanisms are discussed. It is suggested that these drugs may ultimately be particularly indicated in the hypertensive subject with complicating coronary artery disease.

References

1. Nussbaum, H. E., Leff, W., Mattin, V. D., Jr. and Hillman, E. The effects of iproniazid phosphate (Marsilid) on hypertension. *Angiology*, 8: 198, 1957.
2. Harnes, J. The effect of Marsilid on blood pressure in hypertensive patients. *J. Clin. & Exper. Psycopath.*, 19: 152, 1958.
3. Hollander, W. and Wilkins, R. W. Iproniazid and other amine oxidase inhibitors in arterial hypertension with or without complicating angina pectoris. In: Hypertension: The First Hahnemann Symposium on Hypertensive Disease, p. 399. Edited by J. H. Mayer. Philadelphia, 1959. W. B. Saunders Co.
4. Gillespie, L., Terry, L. L. and Sjoerdsma, A. The application of a monoamine-oxidase inhibitor, 1-phenyl-2-hydrazinepropane (JB-516), to the treatment of primary hypertension. *Am. Heart J.*, 58: 1, 1959.
5. Zetzel, L. and Kaplan, H. Liver damage concurrent with iproniazid administration. *New England J. Med.*, 258: 1209, 1958.
6. Pletscher, A. and Pellmont, B. Biological and pharmacologic actions of Marsilid on the heart. *J. Clin. & Exper. Psychopath.*, 19: 163, 1958.
7. Undenfriend, S., Weissbach, H. and Bogdanski, D. F. Effect of iproniazid on serotonin metabolism in vivo. *J. Pharm. & Exper. Therap.*, 120: 255, 1957.
8. Friend, D. G., Serif Zileli, M., Hamlin, J. T. and Reutter, F. W. The effect of iproniazid on the inactivation of norepinephrine in the human. *J. Clin. & Exper. Psycopath.*, 19: 61, 1958.
9. Brodie, B. B. Effects of chlorpromazine, reserpine and monoamine oxidase inhibitors on the cardiovascular system by interaction with central and peripheral neurohumoral agents. Proceedings of the Council for High Blood Pressure Research, vol. 10, 1958.

Monoamine Oxidase Inhibitors in Hypertension*

MORTON H. MAXWELL, M.D., HAROLD BERNSTEIN, M.D., SAMUEL ROTH, M.D. *and* CHARLES R. KLEEMAN, M.D.

Los Angeles, California

WHEN the early monoamine oxidase inhibitors, isoniazid and iproniazid, were introduced as antituberculous and antidepressant agents, postural hypotension was often noted.[1,2] Subsequent studies[3–6] of hypertensive patients indicated a mild hypotensive effect in supine blood pressure and moderate to severe lowering of standing blood pressure (Table 1). Although iproniazid seemed to show considerable promise as a possible antihypertensive agent, unpleasant side effects were frequently noted. Its clinical use was abandoned when reports of serious and even fatal liver damage appeared in 1958.[7] Subsequently, other analogs of iproniazid, believed to be less toxic, have been studied for their hypotensive properties.

Sjoerdsma and his co-workers[8,9] treated two small groups of hypertensive patients with beta-phenylisopropyl hydrazine (JB-516, Catron®) and noted a mild drop in systolic, diastolic and mean blood pressure in the supine position, and a greater drop in the standing position (Table 1). Average doses were 21 to 28 mg. daily. In reviewing these data, it is apparent that there was some over-all loss of effectiveness between the end of the fourth week and the final week of therapy (50 to 150 days). It is not clear whether this was due to drug tolerance or to the cessation of chlorothiazide administration in some of the patients.

Orvis et al.[10] studied eight patients with moderate hypertension for a period of ten weeks. JB-516 (12.5 mg. daily) alone or combined with chlorothiazide (500 mg. daily) produced a drop of 12 per cent in both sitting and standing mean blood pressure which appeared within one to two weeks. A fatal case of jaundice has been reported[11] in a hypertensive woman being treated with moderately large doses of JB-516. Jaundice and signs of severe hepatitis and liver necrosis appeared during the fifth week.

CLINICAL RESPONSE TO RO4-1038

Our group has reported[12] our experience with a new monoamine oxidase inhibitor, DL-serine-N^2 - isopropylhydrazide monohydrochloride (RO4-1038),† in a group of forty patients with arterial hypertension. From Figure 1 it can be seen that RO4-1038 is related chemically to both iproniazid and JB-516. Thirty-four of these patients were treated as outpatients and six were hospitalized. The outpatients had stable primary hypertension of moderate severity. The six hospitalized patients had severe arterial hypertension, either primary or secondary to chronic renal disease. The dose of RO4-1038 ranged from 5 mg. every other day to 20 mg. per day. The duration of therapy was two to seven months, with an average of 3.9 months.

Blood Pressure Effects: Twenty outpatients were treated with RO4-1038 only, in an average dosage of 11.2 mg. per day. These had a drop in mean supine and standing pressures of 7.5 and 19.8 per cent, respectively. Fourteen outpatients were treated with an average of 10 mg. of RO4-1038 plus 750 mg. of chlorothiazide daily. In these patients the declines were 21.0 and 32.0 per cent, respectively (Table II). It is of interest that chlorothiazide had a relatively greater potentiating effect on the supine than on the upright blood pressure. The six hospitalized patients received an average of 10 mg. of RO4-1038 daily; all but one also received chloro-

† Supplied by the Department of Clinical Investigation, Hoffmann-La Roche, Inc., Nutley, N. J.

* From the Department of Medicine, University of California Medical Center, and Wadsworth Hospital, Veterans Administration Center, Los Angeles, California.

TABLE I

Summary of Available Data on Comparative Effects of Monoamine Oxidase Inhibitors in Hypertension

References	Patients (no.)	Drug	Average Dose (mg./day)	Drop in Mean Blood Pressure (%)			Comments
				Supine	Sitting	Standing	
Nussbaum et al.[3,4]	22	IPN†	150	?	?	?	77% of patients tested had a mean blood pressure drop of at least 20 mm. Hg; primarily orthostatic
Harnes[6]	17	IPN	250	?	?	?	30% of patients had supine effect. 90% of patients had orthostatic effect
Cesarman[5]	191	IPN	150	5 (?)		10 (?)	34.5% of patients were hypertensive; orthostatic decrease in blood pressure in 70%
Gillespie et al.[8]	10	JB‡	21	2.1		10.0	
	2	JB + C	12.5 + 750	8.0		10.0	
Sjoerdsma et al.[9]	9*	JB	28.5	4.8		29.6	
Orvis et al.[10]	8	IPN	150		16.3	20.0	Same 8 patients used through entire study; supine blood pressures not reported
	8	IPN + C	75 + 1000		21.3	20.7	
	8	IPN	75		10.6	8.5	
	8	JB	12.5		12.1	12.1	
	8	JB + C	12.5 + 500		12.1	11.3	
Present series	20	RO§	11.2	7.5		19.8	
	14	RO + C	10	21.1		32.0	
	6*	RO + C‖	10 + 750	31.0		37.0	

* Hospitalized patients.
† IPN = iproniazid.
‡ JB = Catron®.
§ RO = RO4-1038.
‖ C = chlorothiazide.

thiazide 750 mg. daily (average). As in the study by Sjoerdsma et al.,[9] the greatest hypotensive effect was seen in hospitalized patients. Among these, the mean blood pressure drops were 31 and 37 per cent in the supine and standing positions, respectively (Table III). In the light of numerous studies upon the effects of hospitalization and bedrest *per se* on "basal" blood pressure, such effect must be taken into account in noting the apparently greater response of the hospitalized patients. It must also be pointed out, however, that these were the more severely hypertensive among the patients studied by Maxwell et al.

The initial decrease in blood pressure was found to occur in three to ten days, generally reaching its trough in two to four weeks. The orthostatic hypotensive effect was found to persist for up to three weeks following discontinuance of the drug. Figure 2 is a summary of

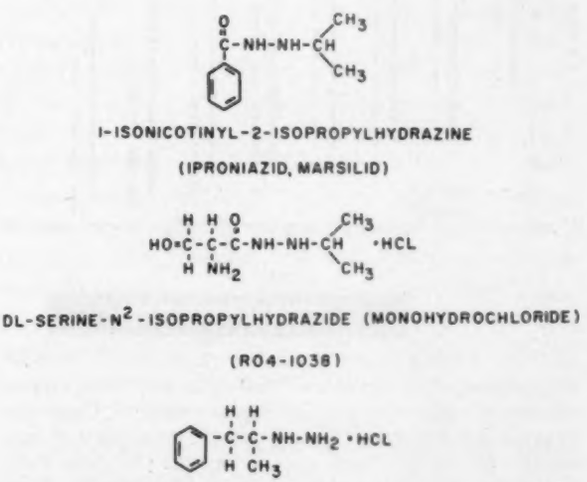


FIG. 1. Structural formulas of three long-acting monoamine oxidase inhibitors.

TABLE II
Blood Pressure Response to RO4-1038—Outpatients

Therapy	No.	Average Blood Pressure (mm. Hg)		Mean Blood Pressure (mm. Hg)		
		Control	Drug	Control	Drug	Change (%)
Supine						
All patients	34	198/110	161/93	139.4	115.8	−17.1
MAOI*	20	190/105	174/98	133.2	123.1	− 7.5
MAOI + C†	14	215/121	160/100	152.6	120.4	−21.1
Standing						
All patients	34	195/117	134/89	142.0	104.0	−26.8
MAOI	20	186/114	144/95	138.2	111.4	−19.8
MAOI + C	14	211/126	133/89	153.9	104.2	−32.0

* MAOI = RO4-1038.
† C = chlorothiazide.

the blood pressure response of a fairly typical patient, who in this particular case had hypertension secondary to polycystic kidney disease (serum creatinine 2.8 mg. per cent).

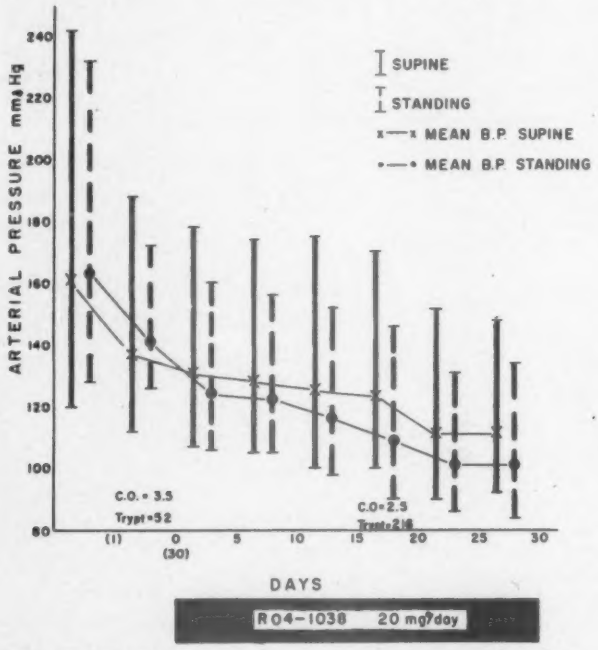


FIG. 2. Typical blood pressure response to RO4-1038. Patient had hypertension secondary to polycystic kidney disease (serum creatinine 2.8 mg. per cent). There is a gradual diminution in blood pressure, reaching a trough by the end of the third week. Beyond this time there was no further decrease in mean blood pressure. Note the greater orthostatic than supine response. The initial decrease in blood pressure before drug therapy was started occurred during thirty days of bed rest in the hospital. Cardiac outputs (C.O.) and urinary tryptamine excretions (Trypt.) are indicated.

Side Effects: All patients were followed with frequent blood counts, urinalyses and determinations of serum creatinine, transaminase, bilirubin and BSP excretion. No evidence of blood, renal or hepatic toxicity was noted. Parasympatholytic side effects were not encountered. No visual difficulties, such as red-green color blindness or blurring, were observed. Occasional mild insomnia and increased sweating about the head and neck were noted. Most of the patients had an increased sense of well being and energy.

Summary of Clinical Results: Table I presents a resume of the available clinical data on the use of monoamine oxidase inhibitors in human arterial hypertension, and to some extent permits comparison among these as to dose and general effectiveness. All but fifteen of the observed patients were studied on an outpatient basis. It is apparent from this table that the new monoamine oxidase inhibitor, RO4-1038, is as effective in small doses as much higher

TABLE III
Changes in Blood Pressure in Six Hospitalized Patients

Position	Average Blood Pressure (mm. Hg)		Mean Blood Pressure (mm. Hg)		
	Control	Drugs*	Control	Drugs*	Change (%)
Supine	217/127	145/90	157	108	−31
Standing	199/123	112/80	145	91	−37

* RO4-1038, average of 10 mg. daily, combined with chlorothiazide 750 mg. daily in five cases.

TABLE IV
Lack of Relationship between Hypotensive Action and Monoamine Oxidase Inhibiting Properties

Drug	Dose (mg./day)	Patients (no.)	Decrease in Mean Standing Blood Pressure (%)	Dose Response (% change per drug)	MAOI*
Iproniazid	150	8	20	0.13	1.0
JB-516	15.5	18	10	0.65	10–40
RO4-1038	11.2	20	19.8	1.8	1.5

* Relative monoamine oxidase inhibiting properties *in vitro*, expressed as arbitrary units with iproniazid = 1.0.

doses of iproniazid and is somewhat more effective than equal doses of JB-516. When used in combination with chlorothiazide, excellent blood pressure responses were obtained both in hospitalized and ambulatory patients receiving small average doses of RO4-1038.

It is apparent that because of the small number of patients studied, the relatively short duration of therapy and the lack of comparable criteria and methods of reporting, these conclusions must be regarded as tentative. There are no data as yet regarding the incidence of drug tolerance with long term therapy, or the potentiation of the monoamine oxidase inhibitors with other hypotensive drugs (hydralazine, reserpine and others). To date we have studied sixty hypertensive patients followed up as long as eleven months.[13] We have found (1) no evidence of hepatic toxicity, (2) occasional tolerance to RO4-1038, evidenced by the necessity for increased dosage to maintain the hypotensive effect, and (3) no documented tolerance to the combination of RO4-1038 and chlorothiazide. Since hypertension can never truly be regarded as a stable disorder, the evidence of "tolerance" to RO4-1038 may simply represent worsening of the underlying disease in some patients. Final conclusions regarding tolerance must therefore be withheld until sufficient statistical data are accumulated.

MECHANISM OF HYPOTENSIVE EFFECTS OF MAO INHIBITORS

The hemodynamic mechanism by which the monoamine oxidase inhibitors produce hypotension is unsettled. Neither JB-516 nor RO4-1038 has a depressor effect when administered to dogs. Iproniazid has been shown to cause adrenergic blockade *in vitro*.[14] Preliminary studies in human subjects suggest that RO4-1038 acts primarily by decreasing peripheral resistance, but also reduces cardiac output, especially in the erect position.[15] These hemodynamic effects can be contrasted to those exhibited by the ganglionic blockers, which cause a decreased cardiac output without a change in peripheral resistance; and to hydralazine, which results in an increased cardiac output and greatly decreased resistance.

A question which has intrigued investigators in this field has been whether or not the antihypertensive properties of these compounds were related to their monoamine oxidase inhibiting properties. Unfortunately, this problem still remains unsettled. Spector et al.[16] showed that rabbits given large daily doses subcutaneously (25 mg./kg. body weight) of iproniazid had a doubling of brain serotonin after about three days. Spector[17] also showed that 3 to 10 mg./kg. of JB-516 induced a doubling of rabbit brain serotonin within one hour. Horita[18] stated that JB-516 is roughly ten to forty times more potent than iproniazid in inhibiting serotonin *in vitro* in homogenates of rat brain and liver. Based on the elevation of serotonin content of brains of rats, mice and rabbits, with equal weights of RO4-1038 and iproniazid, RO4-1038 was found to be about one and one-half times as effective a monoamine oxidase inhibitor as iproniazid.[19]

Correlation of MAO Potency and Hypotensive Property: Table IV summarizes the relative clinical effectiveness of iproniazid, JB-516 and RO4-1038, each used alone, as antihypertensive agents. The pooled data are from the articles cited in Table I. The small number of patients shown indicates the paucity of precise information in the literature to date. Hospitalized patients were excluded from this table for reasons cited previously. Only standing blood pressures were used because (1) the most information was available and (2) the monoamine oxidase inhibitors result primarily in postural hypotension. The column labelled

Dose Response expresses the hypotensive effect as percentage drop in mean standing blood pressure which is produced per milligram of drug, (e.g., 1 mg. of iproniazid causes a 0.13 per cent decrease in mean standing blood pressure). Similarly, the relative effectiveness of each agent as an *in vitro* monoamine oxidase inhibitor, as judged by the brain and liver serotonin levels in the rabbit, rat and mouse, is listed under the column labelled MAOI. In this case, iproniazid is used as the standard, and its monoamine oxidase inhibiting properties are arbitrarily given a value of one for purposes of comparison. On a milligram for milligram basis, RO4-1038 is approximately fourteen times as effective as iproniazid and three times as effective as JB-516 in reducing blood pressure. When these figures are then divided by the figures representing their relative monoamine oxidase inhibiting properties (Dose-Response/MAOI), it is evident that there is no apparent correlation between the antihypertensive properties of these agents and their potency as monoamine oxidase inhibitors. That the hypotensive effects of these drugs may be unrelated to their monoamine oxidase inhibiting properties is strengthened by the lack of correlation between hypotension and monoamine oxidase inhibition in individual patients receiving JB-516[9] or RO4-1038.[13]

Summary

1. A survey of the literature reveals that the monoamine oxidase inhibitors, 1-isonicotinyl-2-isopropyl hydrazine (iproniazid, Marsilid), beta-phenylisopropyl-hydrazine hydrochloride (JB-516, Catron®) and DL-serine-N²-isopropyl hydrazide monohydrochloride (RO4-1038), have antihypertensive effects in man.

2. The monoamine oxidase inhibitors cause primarily postural hypotension and in general are potentiated by the simultaneous administration of chlorothiazide. Their cumulative action permits continuous control of hypertension with infrequent dosage but also creates the danger of prolonged hypotension following overdosage.

3. Their antihypertensive action could not be correlated with their relative potency as monoamine oxidase inhibitors.

4. RO4-1038 appears to be the most effective hypotensive agent and from preliminary observations is without serious side effects or major toxicity in the doses used.

5. The monoamine oxidase inhibitors will probably have an important place in the therapy of hypertension.

References

1. O'Connor, J. B., Howlett, K. S., Jr. and Wagner, R. R. Side effects accompanying use of iproniazide. *Am. Rev. Tuberc.*, 68: 270, 1953.
2. Reilly, R. H., Killam, K. F., Jeriney, E. H., Marshall, W. H., Taussig, T., Apter, N. S. and Pfeiffer, C. C. Convulsant effects of isoniazid. J.A.M.A., 152: 1317, 1953.
3. Nussbaum, H. E., Leff, W., Mattia, V. D. and Hillman, E. The effects of iproniazid phosphate (Marsilid) on hypertension; preliminary report. *Angiology*, 8: 198, 1957.
4. Nussbaum, H. E. Discussion of article by Harnes, J. *J. Clin. & Exper. Psychopath.* (sp. suppl.), 19: 162, 1958.
5. Cesarman, T. Iproniazid in cardiovascular therapy, with special reference to its action in angina pectoris and blood pressure. *Ann. N. Y. Acad. Sc.*, 80: 988, 1959.
6. Harnes, J. The effect of marsilid on blood pressure in hypertensive patients. *J. Clin. & Exper. Psychopath.* (sp. suppl.), 19: 152, 1958.
7. Floody, R. J., Dixon, R. E. and Mattia, V. D. Marsilid toxicity; (a preliminary report). *Dis. Nerv. System*, 19: 1, 1958.
8. Gillespie, L., Terry, L. L. and Sjoerdsma, A. Application of a monoamine oxidase inhibitor, 1-phenyl-2-hydrazinopropane (JB-516), to the treatment of primary hypertension. *Am. Heart J.*, 58: 1, 1959.
9. Sjoerdsma, A., Gillespie, L. and Udenfriend, S. A method for measurement of monoamine oxidase inhibition in man: application to studies on hypertension. *Ann. N. Y. Acad. Sc.*, 80: 969, 1959.
10. Orvis, H. H., Tamagna, I. G. and Thomas, R. E. Evaluation of two monoamine oxidase inhibitors in the therapy of arterial hypertension. *Am. J. M. Sc.*, 238: 118, 1959.
11. Beer, D. T. and Schaffner, F. Fatal jaundice after administration of beta-phenylisopropylhydrazine. *J.A.M.A.*, 171: 887, 1959.
12. Maxwell, M. H., Gonick, H. C., Roth, S., Pearce, M. L. and Kleeman, C. R. Hypotensive properties of a new monoamine oxidase inhibitor, DL - serine - N² - isopropylhydrazide monohydrochloride (RO4-1038) (abstract). Presented at Hypertension Symposium, Scientific Sessions, American Heart Association, Philadelphia, October 1959.
13. Maxwell, M. H., Roth, S., Gonick, H. C., Pearce, M. L. and Kleeman, C. R. Clinical evaluation of a new antihypertensive agent: DL-serine-N²-isopropylhydrazide monohydrochloride (RO4-1038). In preparation.
14. Grieseiner, E. C., Dragstedt, C. A., Wells, J. A. and Zeller, E. A. Adrenergic blockade by iproniazid. *Experientia*, 16: 182, 1955.
15. Maxwell, M. H., Scaduto, L., Gonick, H. C., Kleeman, C. R. and Pearce, M. L. Hemodynamic properties of a new monoamine oxidase in-

hibitor, DL-serine-N²-isopropylhydrazide monohydrochloride. In preparation.

16. Spector, S., Prockop, D. and Shore, P. A. Effects of iproniazide and other monoamine inhibitors on norepinephrine and serotonin in brain. *J. Pharmacol. & Exper. Therap.*, 122: 71a, 1958.
17. Spector, S., Shore, P. A. and Brodie, B. B. Presented at Am. Soc. for Pharmacol. & Exper. Therap. (abstract) Ann Arbor, Mich., August, 1958.
18. Horita, A. Beta-phenylisopropylhydrazine, a potent and long acting monoamine oxidase inhibitor. *J. Pharmacol. & Exper. Therap.*, 122: 176, 1958.
19. Clinical data sheet on RO4-1038, Department of Clinical Investigation, Hoffmann-LaRoche, Inc., Nutley 10, New Jersey.

Book Reviews

Metabolism of Cardiac Glycosides. A Review of the Absorption, Metabolism and Excretion of Clinically Important Cardiac Glycosides, by S. C. Wright. Charles C Thomas, Springfield, Ill., 1960, pp. 86, $4.75.

This small monograph, prepared by Dr. Wright of the University of Sydney, Australia, collects many data which are known about cardiac glycosides and presents several new facts. Chemistry, pharmacology, methods of analysis, metabolism, absorption, distribution, excretion and *in vitro* metabolism of the cardiac glycosides are systematically discussed.

The most original chapters are those on the relationship between molecular structure and pharmacologic activity, chromatographic separation of cardiac glycosides and their metabolites and the metabolism of steroids. Urine of treated patients contains digitoxin, digoxin and "metabolite B," the latter in a greater amount than the two former, their ratio being even 80:20.

One important fact which is revealed is the lack of any specific affinity of the cardiac muscle toward the glycosides. Although only those metabolites which still possess an unsaturated lactone ring are cardioactive, the author considers the possibility that the glycosides may be converted to molecules of unknown type, which cannot be detected by the usual biologic or chemical testing methods.

Some well known differences in the pharmacologic behavior of the cardiac glycosides are explained on the basis of the different way in which they are metabolized or excreted. The more polar glycosides are more rapidly excreted in unchanged form, while digitoxin, the least polar, is mostly excreted in the form of cardioactive metabolites.

Experiments with radioactive digitoxin seem to indicate a greater degree of correlation between lipid content of serum protein fractions and the "binding" of digitoxin than between serum albumin and glycoside.

This monograph represents essential reading for anyone interested in the pharmacology of digitalis.

A. A. Luisada, M.D.

Differentialdiagnose innerer Krankheiten. Eine kurzgefasste Darstellung für Ärzte und Studierende, 7th ed., by Robert Hegglin. Georg Thieme Verlag, Stuttgart, 1960, pp. 913, DM 79.50 ($18.95).

This is an important book and should be available in the English language. Since 1952 seven editions have appeared in German and it has been translated into four other languages. The reviewer remembers well the pleasure and information he received from reading the book by Mathes on the same subject. Dr. Hegglin's book is certainly on the same level. It is written by an outstanding and experienced clinician with a full knowledge of the aid he can receive from the laboratory. Whether one reads the chapters on headache or dyspnea, on cyanosis or enlarged hili, or on enlarged lymph nodes or loss of consciousness, the beginner and the advanced student of medicine will receive useful information. An added advantage of this book is the description of rare diseases and syndromes in which Swiss clinicians often excel. The style of writing is pleasing and the printing of the book and illustrations are excellent. It is warmly recommended.

David Scherf, M.D.

EKG-Fibel, ed. by Rolf Heinecker. Georg Thieme Verlag, Stuttgart, 1960, pp. 235, DM 19.80 ($4.70).

This is a well written and modern short presentation of electrocardiography. Since it is all-inclusive only a few lines can be devoted to important disturbances such as parasystole. The author considers incomplete bundle branch block common. Following the nomenclature introduced by Wenckebach and Winterberg and adopted by others, extrasystoles are called active ectopic rhythms. This is somewhat confusing since they are certainly elicited by the preceding beat and are therefore "passive." This small book contains 204 illustrations and thirty-four graphs which are well selected. They are on a small scale and the time lines are almost invisible; therefore, they have to be studied with a magnifying glass. Books of this

type do not enable one to learn electrocardiography but, in conjunction with a course on this subject, they serve well in summarizing the essential points. DAVID SCHERF, M.D.

RECEIVED FOR REVIEW

All books received will be acknowledged in this column. Insofar as possible, as space permits, books of special interest will receive more extensive reviews.

Grundriss und Atlas der Elektrokardiographie, by Rudolf Zuckermann. Georg Thieme Verlag, Leipzig, 1959, pp. 660, DM 72.15.

Current Therapy—1960. Latest Approved Methods of Treatment for the Practicing Physician, edited by Howard F. Conn. W. B. Saunders Co., 1960, pp. 808, $12.00.

Cardiac Resuscitation, edited by J. Willis Hurst. Charles C Thomas, Springfield, 1960, pp. 141, $5.50.

New Methods of Studying Gaseous Exchange and Pulmonary Function, by Alfred Fleisch. Charles C Thomas, Springfield, 1960, pp. 116, $5.75.

The Low Sodium, Fat-Controlled Cookbook, by Alma Smith Payne and Dorothy Callahan. Little, Brown & Co., Boston, 1960, pp. 465, $4.75.

Xylocaine. The Pharmacological Basis of its Clinical Use, by Sten Wiedling. Almqvist & Wiksell, Stockholm, 1959, pp. 146.

Der Funktionelle Bau der Herazkammern, by Alexander Puff. Georg Thieme Verlag, Stuttgart, 1960, pp. 87, DM 18 ($4.30).

Anatomy. A Regional Study of Human Structure, by Ernest Gardner, Donald J. Gray and Ronan O'Rahilly. W. B. Saunders Co., 1960, pp. 999, $15.00.

Blood Pressure Sounds and Their Meanings. Part II. Aetiology of Melanotic Cancer, by John Erskine Malcolm. Charles C Thomas, Springfield, 1960, pp. 70, $3.00.

The Metabolism of Cardiac Glycosides. A Review of the Absorption, Metabolism and Excretion of Clinically Important Cardiac Glycosides, by S. E. Wright. Charles C Thomas, Springfield, 1960, pp. 86, $4.75.

Der Arbeits-und Trainingseinfluss auf Kreislauf und Atmung, by W. Hollmann. Dr. Dietrich Steinkopff Verlag, Stuttgart, 1959, pp. 202, DM 37.50.

Rheographie. Eine Methode zur Beurteilung peripherer Gefässe, by K. Kaindl, K. Polzer and F. Schuhfried. Dr. Dietrich Steinkopff Verlag, Stuttgart, 1959, pp. 109, DM 27.50.

Myocardosis. Pathogenesis, Clinical Aspects and Therapy Concerning the Principles of Metabolic Electrocardiography, by Ferdinand Wuhrmann. Charles C Thomas, Springfield, 1960, pp. 218, $10.50.

Electrocardiographic Techniques. A Manual for Physicians, Nurses and Technicians, second edition, by Kurt Schnitzer. Grune & Stratton, New York, 1960, pp. 109, $4.75.

EKG Fibel, by Rolf Heinecker. Georg Thieme Verlag, Stuttgart, 1960, pp. 235, DM 19.80 ($4.70).

Differentialdiagnose innerer Krankheiten. Eine Kurzgefasste Darstellung für Ärzte und Studierendl, by Robert Hegglin. Georg Thieme Verlag, Stuttgart, 1960, pp. 913, DM 79.50 ($18.95).

Electrophysiology of the Heart, by Brian F. Hoffman and Paul F. Cranefield. McGraw-Hill Book Company, Inc., New York, 1960, pp. 323, $12.50.

Fundamentals of Clinical Hematology, by Byrd S. Leavell and Oscar A. Thorup, Jr. W. B. Saunders Co., Philadelphia, 1960, pp. 503.

Edema. Mechanisms and Management. A Hahnemann Symposium on Salt and Water Retention, edited by John H. Moyer and Morton Fuchs. W. B. Saunders Co., Philadelphia, 1960, pp. 833.

A Primer of Electrocardiography, fourth edition, by George E. Burch and Travis Winsor. Lea & Febiger, Philadelphia, 1960, pp. 293, $5.00.

The Concise Encyclopedia of Modern Surgery, by James Hale Rutledge. Chilton Company, Philadelphia, 1960, pp. 308, $8.00

The Office Assistant in Medical Practice, by Portia M. Frederick and Carol Towner. W. B. Saunders Co., Philadelphia, 1960, pp. 407, $5.25.

Electrocardiography: Principles and Practice, by Ernest Bloomfield Zeisler, Login Brothers, Chicago, 1960, pp. 374.

Missbildungen des Menschlichen Herzens. Entwicklungsgeschichte und Pathologie, by H. Barthel. Georg Thieme Verlag, Stuttgart, 1960, pp. 240, DM 188 ($44.75).

The Clinical Use of Aldosterone Antagonists, by Frederic C. Bartter. Charles C Thomas, Springfield, 1960, pp. 211, $5.00.

Atrial Septal Defect: An Investigation into the Natural History of a Congenital Heart Disease, by H. Gösta Davidsen. Ejnar Munksgaard, Copenhagen, 1960, pp. 225, D Kroner 50.

Proceedings of a Symposium on Central Nervous System Control of Circulation, edited by Ludwig W. Eichna and Donald G. McQuarrie. The American Physiological Society, Washington, D.C., 1960, pp. 311, $5.00.

Radiation. Use and Control in Industrial Application, by Charles Wesley Shilling. Grune & Stratton, New York, 1960, pp. 223, $6.75.

The Chemistry of Lipids in Health and Disease, by H. K. King. Charles C Thomas, Springfield, 1960, pp. 104, $3.75.

P-Q-R-S-T A Guide to Electrocardiogram Interpretation, fourth edition, by Joseph E. F. Riseman. The Macmillan Co., New York, 1960, pp. 168, $6.50.

Cardiopulmonary Hemodynamics of Chronic Lung Disease, by Carsten Müller. Oslo University Press, Oslo, 1959, pp. 371.

On the Causation of Varicose Veins and Their Prevention and Arrest by Natural Means, by T. L. Cleave. John Wright & Sons, Ltd., Bristol (Williams & Wilkins Co., American agent), pp. 39, $2.50.

College News

President's Column

As you all know, the American College of Cardiology held its Ninth Interim Meeting concurrently with the Thirty-Third Annual Meeting of the American Heart Association in St. Louis on October 21st. One advantage of meeting concurrently is that many of our members are able then to attend the American Heart Scientific Sessions.

On Friday morning we had a joint program on clinical cardiology, and on Friday evening the Fireside Conferences were held jointly. Again it can be said that our Fireside Conferences were a great success. This has been reflected in a number of letters that I have received. One letter writer said that his particular Fireside Conference lasted until 11:45 P.M. One would think that the "fire" would have burned out by then!

The College did have one fine social event and that was the dinner before the Fireside Conferences. There was good attendance at this, and we were honored by having the President-Elect of the American Heart Association, the Medical Director and the Director of Education. Dr. Oglesby Paul, the President-Elect, spoke briefly. It was also very nice to welcome at the dinner two of our Honorary Fellows, Dr. Helen B. Taussig of Baltimore and Dr. George R. Herrmann of Texas.

Although a concurrent meeting has many advantages, it is true that there is some loss of identity as far as the College is concerned, and everything will be done to correct this.

It has been brought to my attention that some of our members are not members of the American Heart Association. I urge all who are not to join their local chapter and support the work of the American Heart Association.

I would like to be able to tell you all the things that happened at the well attended Trustees' Meeting, but there is space here for only a few.

For a long time I have thought that the office of Historian of the College should be created; and as the College will soon be having its Tenth Annual Meeting, it seemed an appropriate time to do this. It was with particular pleasure that, at the Trustees Meeting, Dr. Philip Reichert was appointed Historian, in addition to his work as Executive Director. I can think of no person more suitable for this office. It was of great interest at the meeting to see some of the memorabilia of the early records of the College. This included photographs of the early meetings, programs, rosters, press notices and publications.

The trustees were particularly interested in the progress that has been made in preparation for the Annual Meeting in New York in May 1961. The program committee under the chairmanship of Dr. George C. Griffith has already received a large number of papers and abstracts, all of which are being carefully studied so that we may have the best possible scientific program. We were informed that the Scientific and Commercial Exhibits are well underway. Plans are also going forward for a fine social program for the members and their wives.

A movement has been started to study the possibility of overseas workshops in countries that would be especially benefited by such a program. This is now under study; and if it can be worked out, the College will play a leading role in this program.

The Workshop Program for next year will get off to a wonderful start with a three-day session in Boston at the Peter Bent Brigham Hospital under the general leadership of Drs. Dwight E. Harken and John J. Hartigan. Further information is announced in the Journal, but keep the dates January 11, 12 and 13 open for this workshop.

This gives me an opportunity to wish all of you a Happy Holiday Season.

LOUIS F. BISHOP, M.D.
President

1961 Workshop Program

THIS year's program is limited to a selected schedule of six important workshops which are believed to be particularly attractive to members of the College.

Members of the College are urged to take advantage of this opportunity offered by your Postgraduate Education Committee by communicating with Dr. Philip Reichert, Executive Secretary, 350 Fifth Ave., New York 1, New York, relative to arrangements for participation. Due to the limited number of participants for each workshop, early registration is advised.

Clinical Workshop Program 1961

Date (1961)	Preceptor	Topic	Place	Maximum No. of Participants
January 11, 12, 13	Dr. Dwight E. Harken and associates*	Cardiology: clinical, hemodynamic, electrolyte, chemical and surgical survey	Amphitheater of The Peter Bent Brigham Hospital, Boston, Mass.	30
January 14	Drs. David Littman and Arthur Sasahara	Coronary angiography	Veterans Administration Hospital, West Roxbury 32, Mass.	30
January 21, 22	Dr. E. Sterling Nichol and associates	Acute and life-long anticoagulant therapy routines; care of acute and chronic nonsurgical cardiac problems	Miami Heart Institute, Miami Beach, Fla.	3
March 6	Dr. Louis F. Bishop	Office cardiology	141 East 55th St., New York 22, N. Y.	2
March 30, 31	Dr. Samuel Bellet and associates	Fibrinolysin, cardiac arrhythmias and cardiac catheterization	Heart Station, Philadelphia General Hospital, Philadelphia, Pa.	4
May 2	Dr. Don L. Fisher and associates	Left and right heart catheterization	Cardiopulmonary Laboratory, Allegheny General Hospital, Pittsburgh, Pa.	2

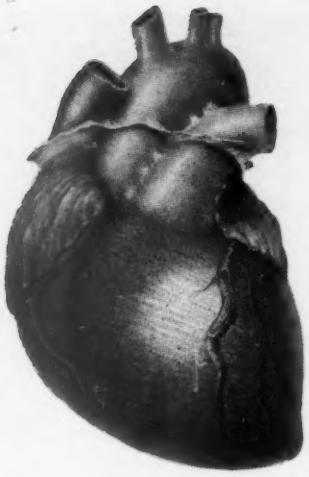
* The following preceptors, in addition to Dr. Harken, will collaborate in this workshop: Samuel A. Levine, M.D., Lewis Dexter, M.D., Laurence B. Ellis, M.D., Richard Gorlin, M.D., Francis D. Moore, M.D., Harold D. Levine, M.D., Bernard Lown, M.D., Warren J. Taylor, M.D. and Armand A. Lefemine, M.D.

AUTHOR INDEX VOLUME VI

SUBJECT INDEX VOLUME VI

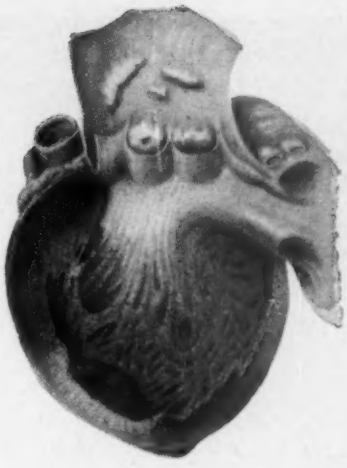
(ab.) = Abstracts; (CR) = Cardiac Resuscitation; (DS) = Diagnostic Shelf; (E) = Editorial; (LE) = Letter to the Editor; (PN) = Progress Notes in Cardiology; (QC) = Query Corner; (WC) = Workmen's Compensation

July (pp. 1–232); August (pp. 233–564); September (pp. 565–704); October (pp. 705–852); November) pp. 853–1002); December (pp. 1003–1164)



IN ANGINA PECTORIS AND CORONARY INSUFFICIENCY

. . . the treatment must go further than vasodilation alone. It should also control the patient's ever-present anxiety about his condition, since anxiety itself may bring on further attacks.



AFTER MYOCARDIAL INFARCTION

. . . it is frequently not enough to boost blood flow through arterial offshoots and establish new circulation. The disabling fear and anxiety that invariably accompany the condition must be reduced, or the patient may become a chronic invalid.

Protects your angina patient better than vasodilators alone

Unless the coronary patient's ever-present anxiety about his condition can be controlled, it can easily induce an anginal attack or, in cases of myocardial infarction, considerably delay recovery.

This is why Miltrate gives better protection for the heart than vasodilation alone in coronary insufficiency, angina pectoris and postmyocardial infarction. Miltrate contains not only PETN (pentaerythritol tetranitrate), acknowledged as basic therapy for long-acting vasodilation. What is more important – Miltrate provides Miltown, a tranquilizer of *proven* effectiveness in relieving anxieties, fear and day-to-day tension in over 600 clinical studies.

Thus, your patient's cardiac reserve is protected against his fear and concern about his condition...and his operative arteries are dilated to enhance myocardial blood supply.

Supplied: Bottles of 50 tablets. Each tablet contains 200 mg. Miltown and 10 mg. pentaerythritol tetranitrate.
Dosage: 1 or 2 tablets q.i.d. *before meals* and at bedtime, according to individual requirements.

REFERENCES

1. Ellis, L. B. *et al.:* Circulation *17*:945, May 1958. **2.** Friedlander, H. S.: Am. J. Cardiol. *1*:395, Mar. 1958. **3.** Riseman, J. E. F.: New England J. Med. *261*:1017, Nov. 12, 1959. **4.** Russek, H. I. *et al.:* Circulation *12*:169, Aug. 1955. **5.** Russek, H. I.: Am. J. Cardiol. *3*:547, April 1959. **6.** Tortora, A. R.: Delaware M. J. *30*:298, Oct. 1958. **7.** Waldman, S. and Pelner, L.: Am. Pract. & Digest Treat. *8*:1075, July 1957.

Miltrate®

Miltown® (meprobamate) + PETN

WALLACE LABORATORIES / *Cranbury, N. J.*

CNL-1388

FOR ANGINA

Nitroglycerin is the drug of choice for the **ACUTE ATTACK**

'CARDILATE'

may well be chosen for **PROLONGED PROPHYLAXIS**

CLINICAL OPINION

"... the magnitude of the response to 15 mg. ['Cardilate'] was comparable to that following nitroglycerin.... The comparatively prolonged duration of action of erythrol tetranitrate when given sublingually makes it especially valuable for clinical use."[1]

CLINICAL OPINION

"Nitroglycerin and erythrol tetranitrate when administered sublingually are among the most potent of all prophylactic agents available for the treatment of patients with angina pectoris."[2]

CLINICAL OPINION

"Erythrol tetranitrate exhibits an inherent long-acting vasodilating effect. Therefore it is the drug of choice in angina pectoris."[3]

'CARDILATE' brand
Erythrol Tetranitrate Sublingual Tablets

NEW

5 mg., scored 

15 mg., scored 

Bottles of 100 tablets.

Complete literature available on request.

1. Riseman, J.E.F., *et al.*: Circulation *17*:22 (Jan.) 1958.

2. Russek, H.I.: Circulation *18*:774 (Oct.) 1958.

3. Hirshleifer, I., *et al.*: Scientific Exhibit, A.M.A., Atlantic City, N. J., June, 1959.

BURROUGHS WELLCOME & CO. (U.S.A.) INC., Tuckahoe, New York

CAMBRIDGE "Versa-Scribe" ELECTROCARDIOGRAPH

CAMBRIDGE
VERSA-SCRIBE
Electrocardiograph
Model VSM (mobile).

WITH SPECIALLY DESIGNED CARRIAGE FOR MOBILE USE

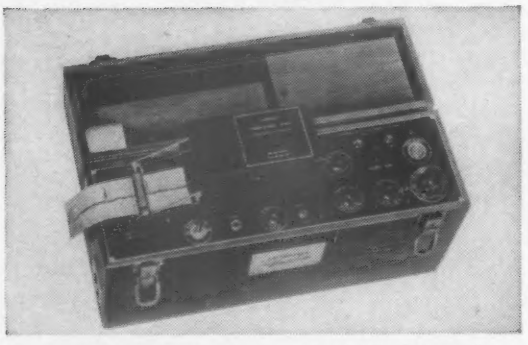
The "Versa-Scribe" fits snuggly into a container which is an integral part of the all-metal carriage . . . no wobbling, nor danger of instrument falling off.

Quiet, widely spaced casters provide an unusually stable stand. Permits easy movement in tight spaces . . . ample storage compartment for accessories.

The "Versa-Scribe" can be easily and quickly removed and inserted into conventional carrying case for use as a portable instrument.

The new "Versa-Scribe" Direct Writer provides dual paper speed, especially valuable in measuring time intervals.

Now more than ever is the Cambridge "Versa-Scribe" the Electrocardiograph of choice.



VERSA-SCRIBE Electrocardiograph Model VS (portable).

Send for descriptive literature

CAMBRIDGE INSTRUMENT CO., Inc.
Graybar Building, 420 Lexington Ave., New York 17, N. Y.

Cleveland 2, Ohio, 8419 Lake Avenue
Detroit 2, Mich., 7410 Woodward Avenue
Oak Park, Ill., 6605 West North Avenue
Jenkintown, Pa., 479 Old York Road
Silver Spring, Md., 933 Gist Avenue

PIONEER MANUFACTURERS OF THE ELECTROCARDIOGRAPH

CAMBRIDGE ALSO MAKES the Audio-Visual Heart Sound Recorder, Multi-Channel Recorder, Dye-Dilution Curve Recorder, Operating Room Cardioscope, "Simpli-Scribe" Direct Writer Electrocardiograph, Pulmonary Function Tester, Educational Cardioscope, Plethysmograph, Electrokymograph, Research pH Meter, Huxley Ultra Microtome, Pocket Dosimeter, and Lindemann-Ryerson Electrometer.

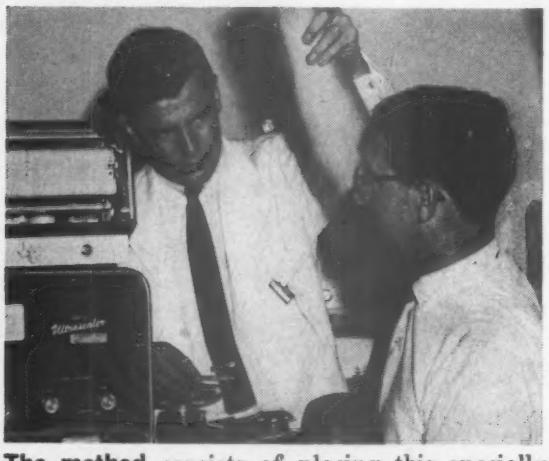
CAMBRIDGE
DIAGNOSTIC INSTRUMENTS

Radioisotopic studies* shed new light on coronary artery disease...

Objective finding – in untreated patients:

In patients with coronary artery disease who receive no therapy, "Myocardial blood flow is significantly... decreased...."[1]

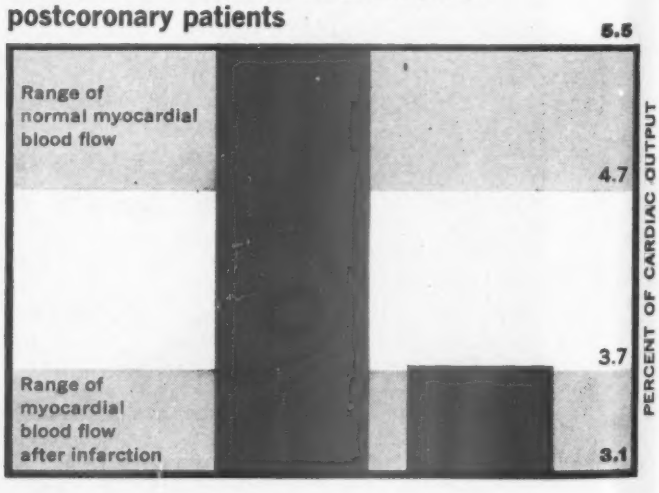
***Important new studies**[1,2] at the University of Oklahoma School of Medicine utilized advanced radioisotopic techniques to measure myocardial blood flow in normal and arteriosclerotic humans.



The method consists of placing this specially designed scintillation detector on the chest wall where it can monitor the passage of radioactive material through the heart and through the myocardial circulation. The new technique appears to be ". . . simple, repeatable, rapid, and nontraumatic. . . ."[2]

The results objectively confirm earlier observations[3,4] that the significant increases in myocardial blood flow produced with PETN (Peritrate) in arteriosclerotic patients lasts as long as five hours after administration.

Myocardial blood flow in normal and postcoronary patients



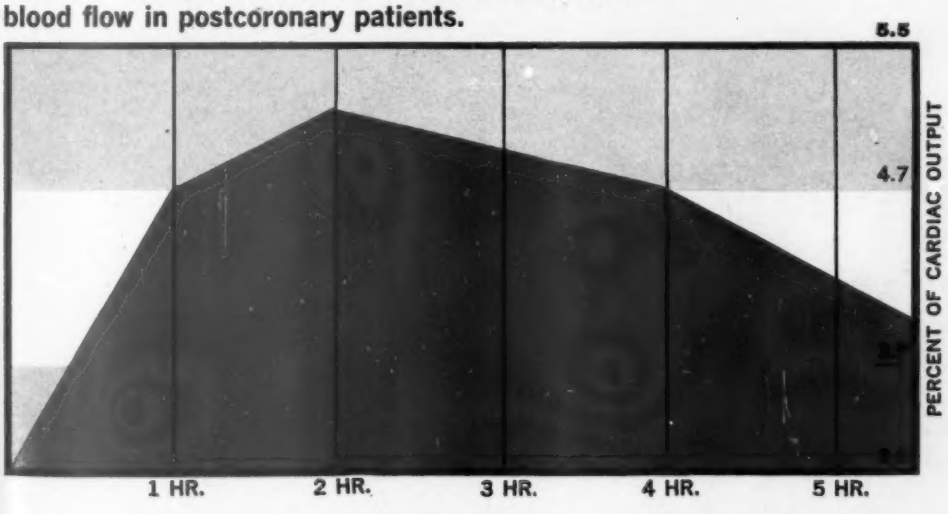
Normal myocardial blood flow ranges between 4.7 and 5.5% of total cardiac output. In patients with previous infarction, myocardial blood flow is significantly decreased to a range of 3.1 to 3.7%.

...reaffirm that Peritrate increases myocardial blood flow

Objective finding – in Peritrate-treated patients:

Peritrate "...produces a prolonged increase in myocardial blood flow beginning within one hour after ingestion and lasting up to five hours, without producing changes in cardiac output, in patients with arteriosclerotic heart disease with previous infarction."[1]

Peritrate safely increases and sustains myocardial blood flow in postcoronary patients.



Within one hour after administration of Peritrate 20 mg., myocardial blood flow returns to near normal range without significant change in cardiac output, blood pressure or pulse rate.

References: 1. Johnson, P. C., and Sevelius, G.: Measurement of myocardial blood flow, J.A.M.A. *173*:1231 (July 16) 1960. 2. Sevelius, G., and Johnson, P. C.: J. Lab. & Clin. Med. *54*:669 (Nov.) 1959. 3. Russek, H. I., *et al.*: Circulation *12*:169 (Aug.) 1955. 4. Essex, H. E., *et al.*: Am. Heart J. *19*:554, 1940.

basic therapy for coronary artery disease —with or without angina

Peritrate®

brand of pentaerythritol tetranitrate

WARNER CHILCOTT

MORRIS PLAINS, N.J.

makers of

TEDRAL GELUSIL

PROLOID

MANDELAMINE

PER CPO 10

MODEL 100M MOBILE VISO-CARDIETTE

$895 delivered,
Continental U.S.A.

THIS IS THE NEWEST Sanborn electrocardiograph — complete with all accessories in a fully mobile, easy-to-roll cabinet version. A single Model 100M "Mobile Viso" can easily serve several locations within a clinic or hospital, and perfectly answers the need for instrument storage away from the point of use. The highly developed design of this modern instrument also provides fully diagnostic cardiograms at either of two chart speeds (25 and 50 mm/sec), sensitivity settings of ½, 1 or 2 times normal, fully automatic stylus stabilization during lead switching, pushbutton grounding, jacks for recording and monitoring non-ECG inputs in conjunction with other equipment. The cabinet is available in either handsome mahogany or exceptionally durable, stain-resistant plastic laminate.

The same basic instrument — with identical circuitry — is also manufactured as a *desk-top instrument*, designated *Model 100 Viso-Cardiette*. A third choice in Sanborn ECG'S is also offered, for the physician whose practice demands *maximum portability:* the 18-pound "briefcase" size *Model 300 Visette*. All are proven Sanborn electrocardiographs, reflecting more than four decades of experience in the manufacture of medical instrumentation.

MEDICAL DIVISION

SANBORN COMPANY

175 WYMAN ST., WALTHAM 54, MASS.

THE FACTS ABOUT MER/29

MER/29 *reduces total body cholesterol in 8 out of 10 —and these are the patients most likely to benefit*

your patient with high cholesterol levels...

MER/29 reduces both serum and tissue cholesterol, irrespective of diet.[1] In 463 patients, the mean cholesterol was reduced from 324 mg.% to 253 mg.% — an average decrease of 71 mg.%.[1-6]

your patient with angina pectoris...

concurrent benefits have been reported in some patients receiving MER/29. These include decreased incidence and severity of attacks, improved ECG patterns, diminished nitroglycerin requirements, and increased sense of well-being.[1,4,6-8]

your patient with postmyocardial infarction...

while more time is needed to determine the over-all prognostic significance, it has been observed that MER/29 "... reduced morbidity and mortality rates below those of control series during the first year following coronary thrombosis."[4]

your patient with generalized atherosclerosis...

atherosclerosis "... has been shown to afflict about 77% of American males as early as in the 20-to-30 age range."[9] With MER/29 you have a new, well-tolerated means of lowering cholesterol — which has been considered "... the *sine qua non* of the atheromatous lesion."[9]

compatible with other cardiovascular therapies: MER/29 can be used along with other measures to control anxiety, hypertension, obesity, and other conditions associated with cardiovascular disorders. These include anticoagulants, nitroglycerin, and PETN.

safety data: Patients have now been treated with MER/29 for relatively long and continuous periods. In no case has there been evidence of serious toxic effects on the function of any vital organ or system. However, since long-term MER/29 therapy may be necessary, periodic examinations, including liver-function tests, are desirable. Side effects (nausea, headache, dermatitis) are rare and have usually been associated with dosages greater than those recommended for effective therapy.

contraindication: Pregnancy. Since MER/29 inhibits cholesterol biosynthesis, and cholesterol plays an important role in the development of the fetus, the drug should not be administered during pregnancy.

supplied: Bottles of 30 pearl gray capsules.

. . . the first cholesterol-lowering agent to inhibit the formation of excess cholesterol within the body, reducing both tissue and serum cholesterol

. . . no demonstrable interference with other vital biochemical processes reported to date

. . . convenient dosage: one 250 mg. capsule daily before breakfast

. . . toleration and absence of toxicity established by 2 years of clinical investigation

MER/29

(triparanol)

References: 1. Hollander, W., and Chobanian, A. V.: Boston M. Quart. *10*:37 (June) 1959. 2. Oaks, W., and Lisan, P.: Fed. Proc. *18*:428 (Mar.) 1959. 3. Oaks, W. W., *et al.*: A. M. A. Arch. Int. Med. *104*:527 (Oct.) 1959. 4. Lisan, P.: Proceedings, Conference on MER/29, Progr. Cardiovasc. Dis. *2*:(Suppl.)618 (May) 1960. 5. Oaks, W. W.: *Ibid.*, p. 612. 6. Hollander, W., *et al.*: *Ibid.*, p. 637. 7. Halperin, M. H.: *Ibid.*, p. 631. 8. Toro, J.: *Ibid.*, p. 544. 9. Morrison, L. M.: J.A.M.A. *173*:884 (June 25) 1960.

Merrell SINCE 1828

THE WM. S. MERRELL COMPANY
Cincinnati 15, Ohio • St. Thomas, Ontario

D-3618

TRADEMARK: "MER/29"

this hypertensive patient prefers Singoserp... and so does his physician

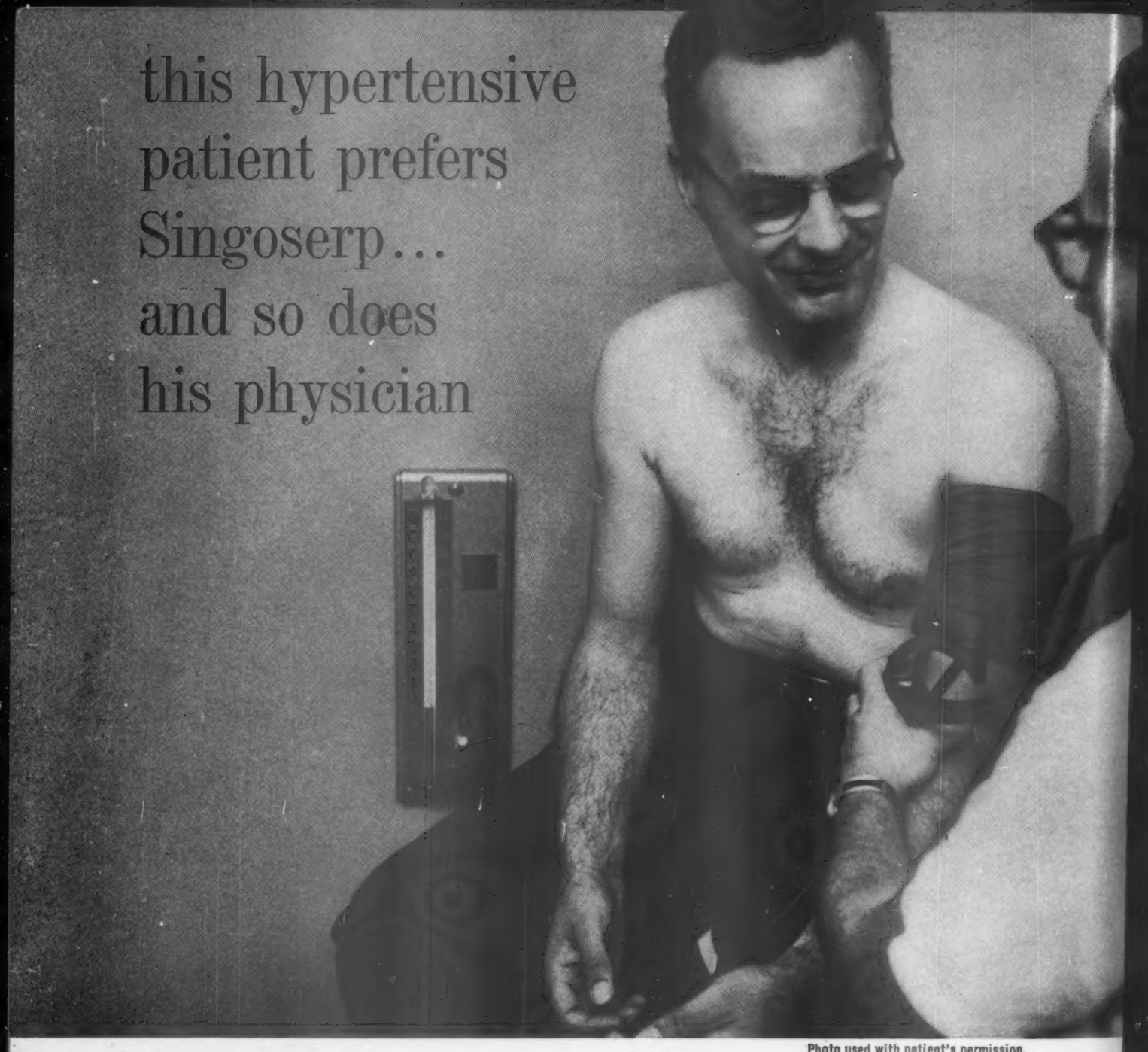


Photo used with patient's permission.

Patient's comment: "The other drug [whole root rauwolfia] made me feel lazy. I just didn't feel in the mood to make my calls. My nose used to get stuffed up, too. This new pill [Singoserp] doesn't give me any trouble at all."

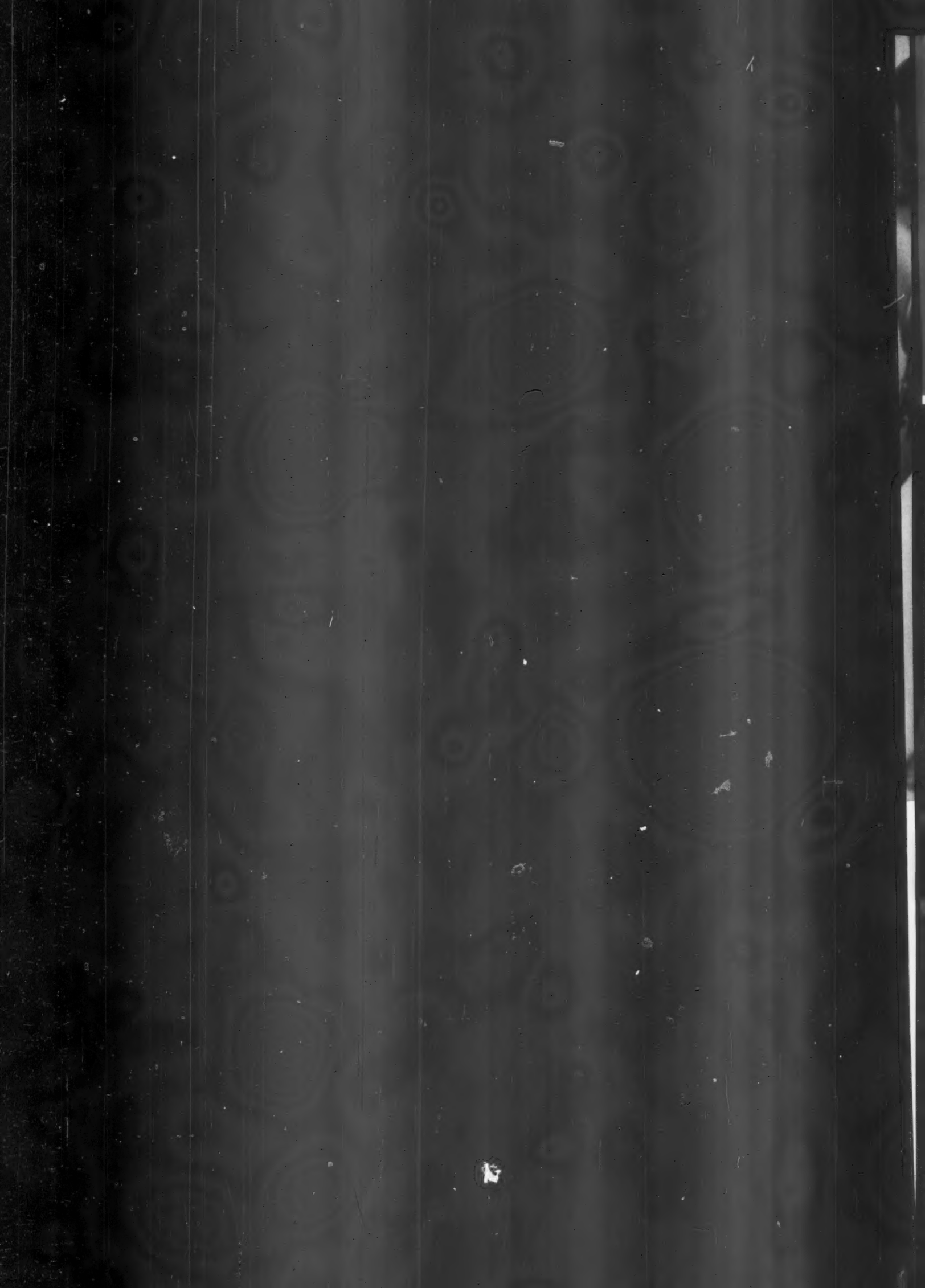
Clinician's report: J. M., a salesman, had a 16-year history of hypertension. Blood pressure at first examination was 190/100 mm. Hg. Whole root rauwolfia lowered pressure to 140/80 — but side effects were intolerable. Singoserp, 0.5 mg. daily, further reduced pressure to 130/80 and eliminated all drug symptoms.

Many hypertensive patients and their physicians prefer Singoserp® because it usually lowers blood pressure without rauwolfia side effects

SUPPLIED: Singoserp **Tablets,** 1 mg. (white, scored). Also available: Singoserp®-Esidrix® **Tablets** #2 (white), each containing 1 mg. Singoserp and 25 mg. Esidrix; Singoserp®-Esidrix® **Tablets** #1 (white), each containing 0.5 mg. Singoserp and 25 mg. Esidrix. **Complete information sent on request.**
Singoserp® (syrosingopine CIBA) **Singoserp®-Esidrix®** (syrosingopine and hydrochlorothiazide CIBA)

2/2644HB

CIBA
SUMMIT, NEW JERSEY



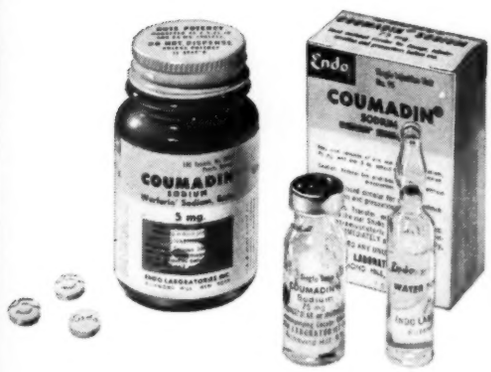
COUMADIN®

the proven anticoagulant

FOR ORAL, INTRAVENOUS OR INTRAMUSCULAR USE

Over 90
published papers
since 1953

131,000,000
Over ~~114,000,000~~
doses administered
to date



now
more widely
prescribed than
all other oral
anticoagulants
combined

the original and only warfarin responsible for establishing this drug as closely approaching the *ideal* anticoagulant.[1,2]

1. Baer, S., et al.: J.A.M.A. 167:704, June 7, 1958.
2. Moser, K. M.: Disease-a-Month, Chicago, Yr. Bk. Pub., Mar., 1960, p. 13.

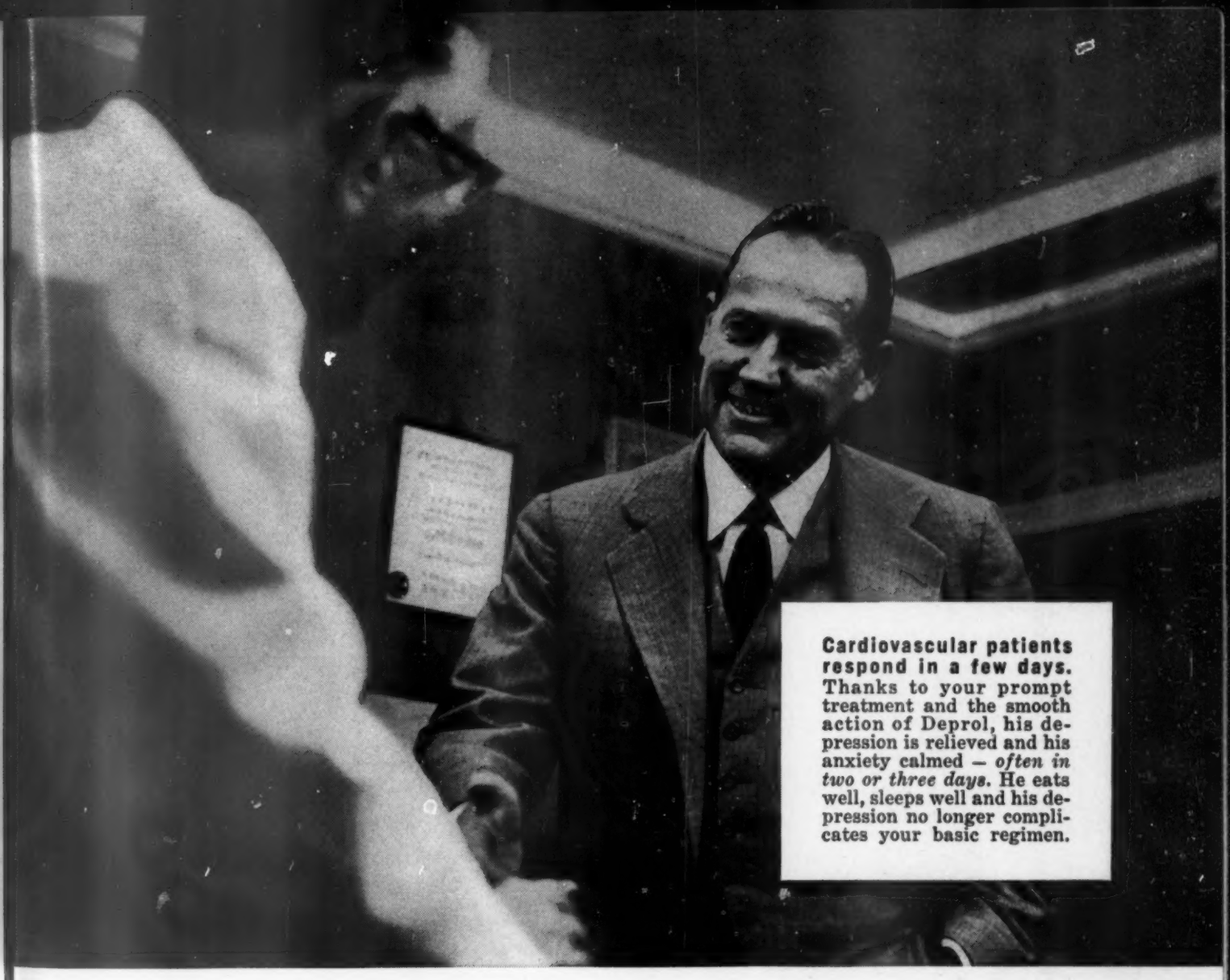
*Manufactured under license from the Wisconsin Alumni Research Foundation

Full range of oral and parenteral dosage forms—COUMADIN* (warfarin sodium) is available as: ***Scored tablets***—2 mg., lavender; 5 mg., peach; 7½ mg., yellow; 10 mg., white; 25 mg., red. ***Single Injection Units***—one vial, 50 mg., and one 2 cc. ampul Water for Injection; one vial, 75 mg., and one 3 cc. Water for Injection.

Average Dose: Initial, 40-60 mg. For elderly and/or debilitated patients, 20-30 mg. ***Maintenance***, 5-10 mg. daily, or as indicated by prothrombin time determinations.

Endo®

Complete Information and Reprints on Request
ENDO LABORATORIES Richmond Hill 18, New York



Cardiovascular patients respond in a few days. Thanks to your prompt treatment and the smooth action of Deprol, his depression is relieved and his anxiety calmed – *often in two or three days.* He eats well, sleeps well and his depression no longer complicates your basic regimen.

Lifts depression...as it calms anxiety!

For cardiovascular patients–a smooth, balanced action that lifts depression as it calms anxiety...rapidly and safely

Balances the mood–no "seesaw" effect of amphetamine-barbiturates and energizers. While amphetamines and energizers may stimulate the patient – *they often aggravate anxiety and tension.* And although amphetamine-barbiturate combinations may counteract excessive stimulation – *they often deepen depression.*

In contrast to such "seesaw" effects, Deprol lifts depression as it calms anxiety – both at the same time.

Acts swiftly–the patient often feels better, sleeps better, within two or three days. Unlike most other antidepressant drugs, Deprol relieves the patient quickly – often within two or three days.

Acts safely – no danger of hypotension. Deprol does not cause hypotension, tachycardia, jitteriness, or liver toxicity. It can be safely administered with basic cardiovascular therapy.

Dosage: Usual starting dose is 1 tablet q.i.d. When necessary, this may be gradually increased up to 3 tablets q.i.d.
Composition: 1 mg. 2-diethylaminoethyl benzilate hydrochloride (benactyzine HCl) and 400 mg. meprobamate.
Supplied: Bottles of 50 light-pink, scored tablets. Write for literature and samples.

Deprol®

WALLACE LABORATORIES
Cranbury, N. J.

CD-768

THE *Yorke* CREED

THE PURPOSE OF the Yorke Medical Group is to contribute to the improvement of human health and well being through the publication of medical research and experiences, as controlled by our Physician-Surgeon Editorial Boards. Our code of conduct shall be—

To obtain the most qualified personnel available to serve on our Editorial Staffs.

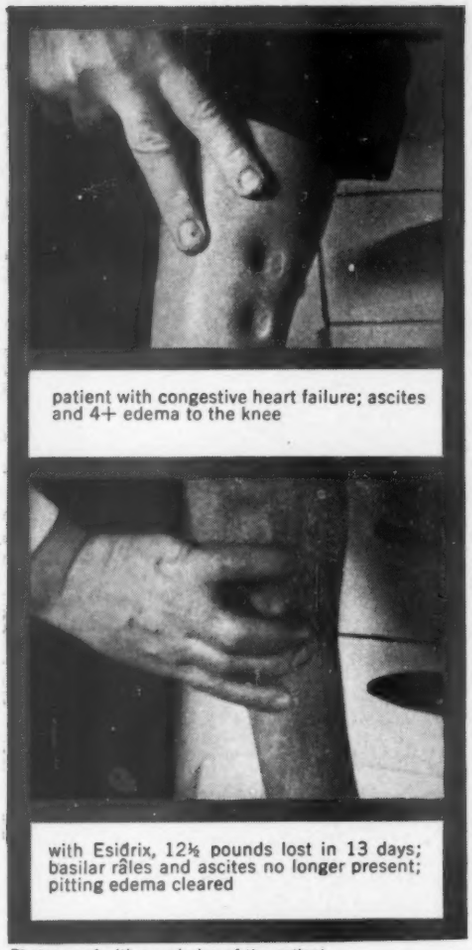
To select material only on the basis of its scientific merit and value to the profession and such selection shall be the sole and exclusive responsibility of the Physicians and Surgeons who comprise the Editorial Boards.

To limit advertising to ethical pharmaceuticals and reputable medical equipment or services of immediate interest to our subscribers. Advertising must be consistent in standards with the editorial policies of the Journals.

Medical journals present the recorded experiences of the profession and serve as a basis for new researches and life preserving developments.

THE YORKE GROUP
NEW YORK, N. Y.

THE AMERICAN JOURNAL OF SURGERY
THE AMERICAN JOURNAL OF MEDICINE
THE AMERICAN JOURNAL OF CLINICAL NUTRITION
THE AMERICAN JOURNAL OF CARDIOLOGY
MODERN DRUGS



patient with congestive heart failure; ascites and 4+ edema to the knee

with Esidrix, 12½ pounds lost in 13 days; basilar râles and ascites no longer present; pitting edema cleared

benefits in edema, benefits in hypertension plus built-in potassium protection

Photos used with permission of the patient.

NEW ESIDRIX-K®

New ESIDRIX-K provides all the oral diuretic-antihypertensive advantages of ESIDRIX, plus a generous potassium supplement. ESIDRIX produces marked excretion of salt and water in edematous patients, and in many hypertensive patients significantly reduces blood pressure, alone or with other antihypertensive drugs. Potassium excretion is minimal, and the built-in K supplement further helps eliminate problems due to potassium loss. Three ESIDRIX-K tablets provide potassium equivalent to one quart of fresh orange juice; ESIDRIX-K is coated to prevent gastric irritation.

Complete information sent on request.

Supplied: Esidrix-K Tablets (white, coated), each containing 25 mg. Esidrix and 500 mg. potassium chloride. Esidrix Tablets, 25 mg. (pink, scored) and 50 mg. (yellow, scored).

Esidrix-K is especially indicated for patients in whom even moderate potassium loss can cause complications, or those whose condition predisposes to hypokalemia. Among candidates for Esidrix-K are patients taking digitalis for congestive heart failure, those with renal or liver disease, those under long-term treatment, and those on salt-restricted diets.

CIBA
SUMMIT, NEW JERSEY

ESIDRIX® (hydrochlorothiazide CIBA)

2/2841MK-2


another patient with hypertension?

indicated in all degrees of hypertension

effective by itself in most hypertensives

HYDROPRES*

HYDRODIURIL® with RESERPINE
(HYDROCHLOROTHIAZIDE)

HYDROPRES can be used:

- *alone* (In most patients, HYDROPRES is the only antihypertensive medication needed.)
- *as basic therapy, adding other drugs if necessary* (Should other antihypertensive agents need to be added, they can be given in much lower than usual dosage so that their side effects are often strikingly reduced.)
- *as replacement therapy, in patients now treated with other drugs* (In patients treated with rauwolfia or its derivatives, HYDROPRES can produce a greater antihypertensive effect. Moreover, HYDROPRES is less likely to cause side effects characteristic of rauwolfia, since the required dosage of reserpine is usually less when given in combination with HydroDIURIL than when given alone.)

HYDROPRES-25
25 mg. HydroDIURIL, 0.125 mg. reserpine.
One tablet one to four times a day.

HYDROPRES-50
50 mg. HydroDIURIL, 0.125 mg. reserpine.
One tablet one or two times a day.

also available: **HYDROPRES-Ka-50**
50 mg. HydroDIURIL, 0.125 mg. reserpine, 572 mg. potassium chloride.
One tablet one or two times a day.

If the patient is receiving ganglion blocking drugs or hydralazine, their dosage must be cut in half when HYDROPRES is added.

For additional information, write Professional Services, Merck Sharp & Dohme, West Point, Pa.

MERCK SHARP & DOHME, DIVISION OF MERCK & CO., INC., WEST POINT, PA.

*HYDROPRES, HYDROPRES-Ka, AND HYDRODIURIL ARE TRADEMARKS OF MERCK & CO., INC.

YOUNG INVESTIGATORS' AWARD

The American College of Cardiology is pleased to announce the establishment of an award for excellence to be entitled:

"THE YOUNG INVESTIGATORS' AWARD OF THE AMERICAN COLLEGE OF CARDIOLOGY"

THIS AWARD IS REPRESENTED BY A SILVER MEDAL AND $1,000.

The conditions of the award are:

ELIGIBILITY Any physician in residency or fellowship status or within 3 years following his residency or fellowship.

SCOPE A formal presentation, 10 minutes in length, describing original investigation in which the contestant did either the work or was a significant member of investigating team.

PROCEDURE An original manuscript and letter indicating intention to enter the competition must be in hands of Executive Director by *March 1, 1961.*

An *accompanying* letter from the chief of the service or laboratory indicating his willingness to have the material presented in the competition.

Judging to be made by the Committee of Judges selected by the President of the American College of Cardiology and their decision to be based upon (a) excellence and orginality of investigation (b) excellence of written manuscript (c) excellence of presentation.

Competition to be in New York City upon the occasion of the 10th Annual Meeting of the American College of Cardiology, date May 17 to 20, 1961.

Address queries and manuscript to: Executive Director, American College of Cardiology, Empire State Building, 350 Fifth Avenue, New York 1, New York.

DRAMATIC
physical and emotional relief in
ANGINA PECTORIS

'round-the-clock protection against both pain and fear

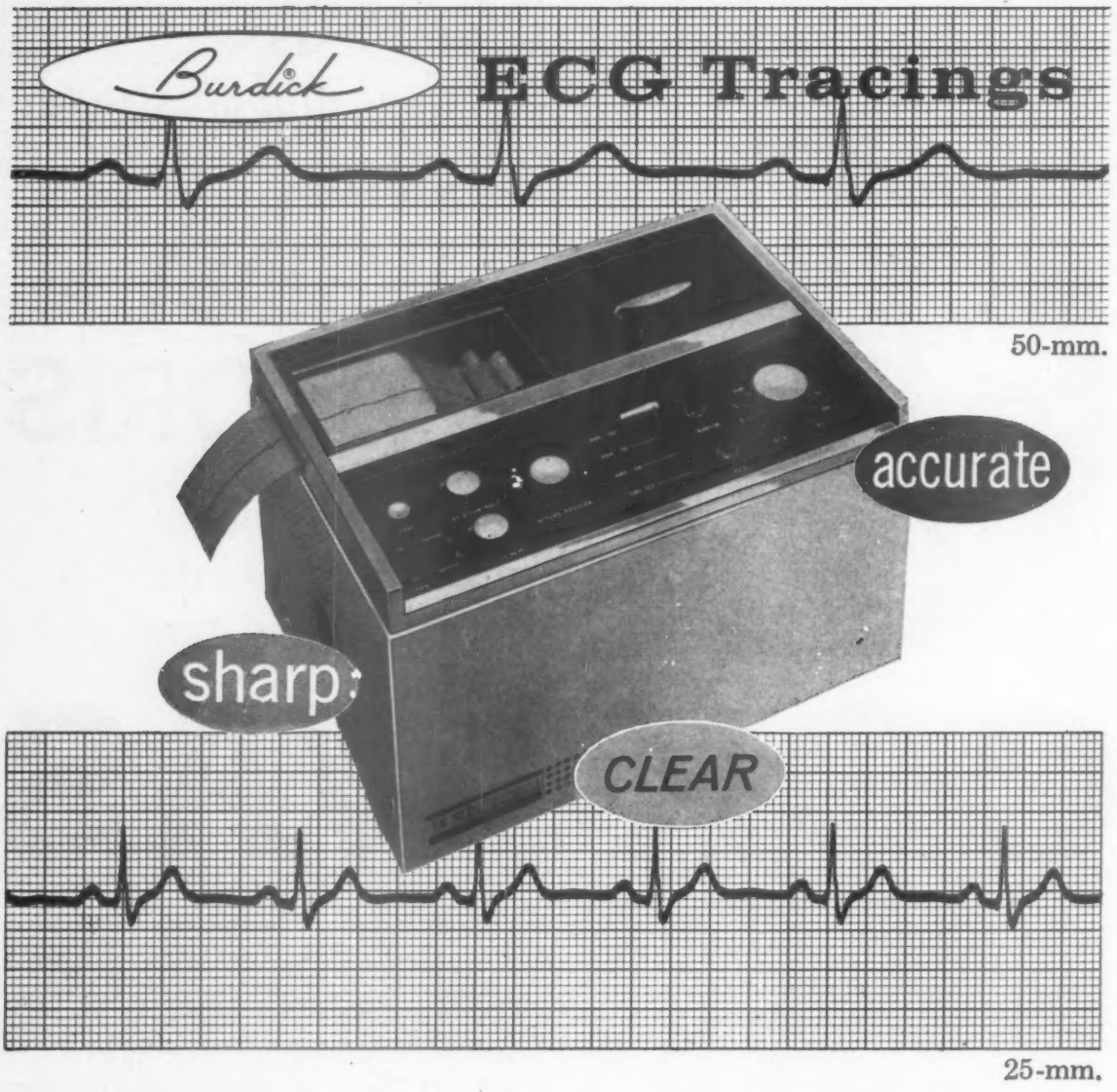
COROVAS
Tymcaps

COROVAS is a nontoxic, uniform-acting, long-acting vasodilator to control or prevent attacks of angina pectoris. One COROVAS Tymcap upon arising provides up to 12 hours of continuous coronary vasodilation, and another COROVAS Tymcap before the evening meal affords maximum protection against seizures all night. COROVAS alleviates the associated fear of pain. Reduces the need for emergency nitroglycerin. Safe and effective for long-term therapy.

SUPPLIED—Boxes of 60 and 120.

PROLONGED, SUSTAINED ACTION OF VASODILATING PENTAERYTHRITOL TETRANITRATE (PETN) 30 MG., AND SEDATIVE SECOBARBITURIC ACID 50 MG. IN EACH COROVAS TYMCAP.

AMFRE GRANT, INC.
Brooklyn 26, N. Y.

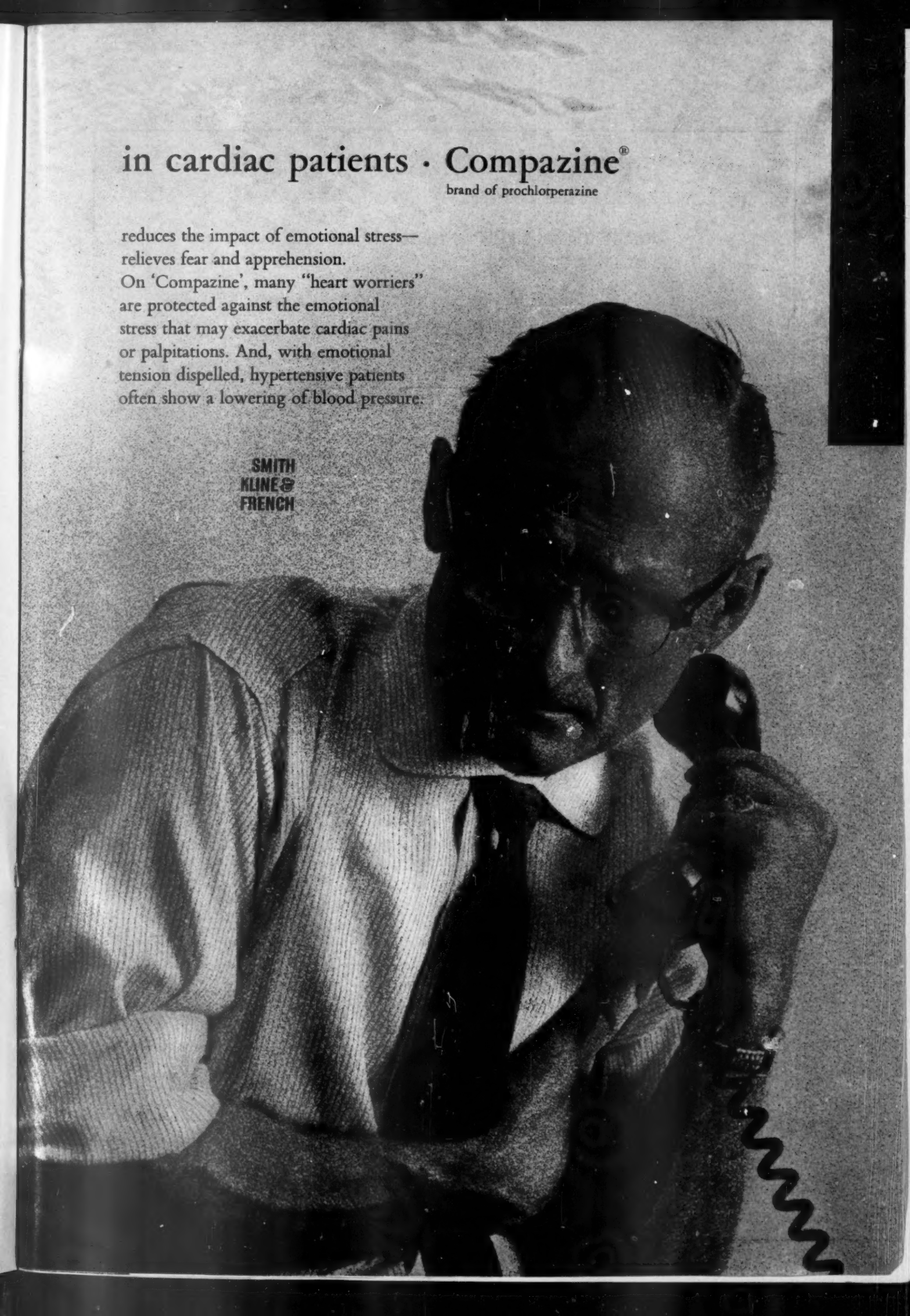


Recent electronic advances—fully incorporated in the new Burdick EK-III Electrocardiograph—permit doctors to obtain ECG tracings of unparalleled clarity and accuracy. Due to better frequency response, diagnostic detail is outstanding at both 25- and 50-mm. per-second speeds. The Burdick EK-III saves time, too. Its stability of operation and fast switching enable the operator to obtain a complete tracing quickly and surely. Let Burdick bring you up to date. See the modern EK-III soon!

Burdick®

THE BURDICK CORPORATION
Milton, Wisconsin

Branch Offices: NEW YORK • CHICAGO • ATLANTA • LOS ANGELES
Dealers in all principal cities


in cardiac patients · Compazine®
brand of prochlorperazine
reduces the impact of emotional stress—
relieves fear and apprehension.
On 'Compazine', many "heart worriers"
are protected against the emotional
stress that may exacerbate cardiac pains
or palpitations. And, with emotional
tension dispelled, hypertensive patients
often show a lowering of blood pressure.
SMITH
KLINE &
FRENCH

CHANGING YOUR ADDRESS?

Please fill out and return the coupon below:

THE AMERICAN JOURNAL OF CARDIOLOGY
Mailing Dept., 11 East 36th Street, New York 16, N. Y.

NAME_____
(please print)

NEW ADDRESS:

Street_____

City_____ Zone_____ State_____

FORMER ADDRESS:

Street_____

City_____ Zone_____ State_____

"Are the xanthines effective in ANGINA PECTORIS ?"

(Abstract of the paper with above title)

A favorable response was unequivocally demonstrated with aminophylline when administered intravenously to angina pectoris patients. In sharp contrast the author, noted for his original contributions to cardiovascular research, found oral administration ineffective in all patients tested. This suggested that the failure was correlated with subthreshold theophylline blood-levels obtained with oral administration.

A 20% alcohol-solution of theophylline (Elixophyllin®) has been shown to provide blood levels comparable to those obtained with I.V. administration of aminophylline. This oral preparation and a placebo (identical in appearance, taste and alcoholic content) were tested by the electrocardiographic response obtained and by a double-blind clinical evaluation.

The author reported: "In the light of these findings, conclusions derived from animal experiments which have classed theophylline as a 'malignant' coronary vasodilator must be rejected for man." Elixophyllin administered orally to 30 patients was effective "not only in control of symptoms but in its modifying action on the electrocardiographic response to standard exercise. The efficacy of this preparation is based on the rapid absorption and attainment of high blood levels made possible by the vehicle employed."

(Russek, H. I., Am. J. Med. Sc. Feb., 1960)

Advertisers' Product Index

December, 1960

*** Complete description of starred drugs will be found in MODERN DRUGS and THE MODERN DRUG ENCYCLOPEDIA**

ADVERTISING REPRESENTATIVES

New York
P. D. Brewer, R. P. Davis, A. K. Detwiller
MUrray Hill 3-2980

Chicago
R. H. Andrew, C. P. Haffner
WAbash 2-7738

safe and practical treatment of the postcoronary patient

A basic characteristic of the postcoronary patient, whether or not cholesterol levels are elevated, is his inability to clear fat from his blood stream as rapidly as the normal subject.[1-3] *Figure #1* graphically illustrates this difference in fat-clearing time by comparing atherosclerotic and normal subjects after a fat meal.[3]

"Slow clearers" gradually accumulate an excess of fat in the blood stream over a period of years as each meal adds an additional burden to an already fat-laden serum. As shown in *figure #2,* the blood literally becomes saturated with large fat particles, presenting a dual hazard to the atherosclerotic patient: the long-term danger of deposition of these fats on the vessel walls,[4] and the more immediate risk of high blood fat levels after a particularly heavy meal possibly precipitating acute coronary embarrassment.[5]

In *figure #3,* the test tube at the left contains lipemic serum, while the one at the right contains clear, or normal serum. If serum examined after a 12-hour fasting period presents a milky appearance, this is a strong indication that the patient clears fat slowly and is a candidate for antilipemic therapy in an effort to check a potentially serious situation.

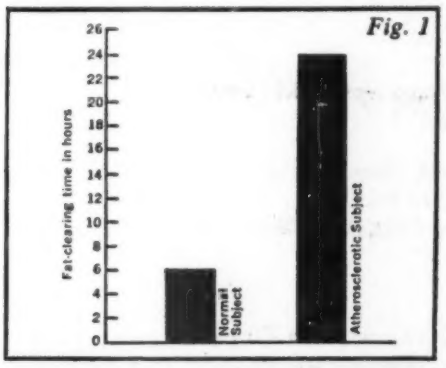
'Clarin', which is heparin in the form of a *sublingual tablet,* has been demonstrated to clear lipemic serum.[2,6,7] Furthermore, a two-year study using matched controls resulted in a statistically significant reduction of recurrent myocardial infarction in 130 patients treated with 'Clarin'.[8]

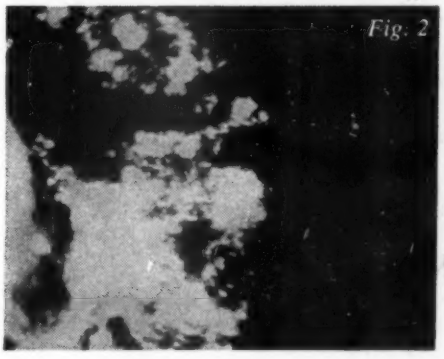
'Clarin' therapy is simple and safe, requiring no clotting-time or prothrombin determinations. Complete literature is available to physicians upon request.

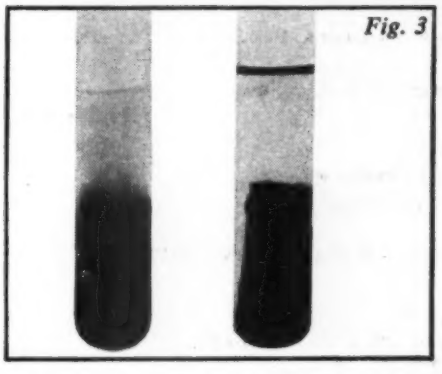
References: 1. Anfinsen, C. B.: Symposium on Atherosclerosis, National Academy of Sciences, National Research Council Publication 338, 1955, p. 218. 2. Berkowitz, D.; Likoff, W., and Spitzer, J. J.: Clin. Res. 7:225 (Apr.) 1959. 3. Stutman, L. J., and George, M.: Clin. Res. 7:225 (Apr.) 1959. 4. Wilkinson, C. F., Jr.: Annals of Int. Med. *45*:674 (Oct.) 1956. 5. Kuo, P. T., and Joyner, C. R., Jr.: J.A.M.A. *163*:727 (March 2) 1957. 6. Fuller, H. L.: Angiology 9:311 (Oct.) 1958. 7. Shaftel, H. E., and Selman, D.: Angiology *10*:131 (June) 1959. 8. Fuller, H. L.: Circulation *20*:699 (Oct.) 1959.

Clarin*

(sublingual heparin potassium, Leeming)







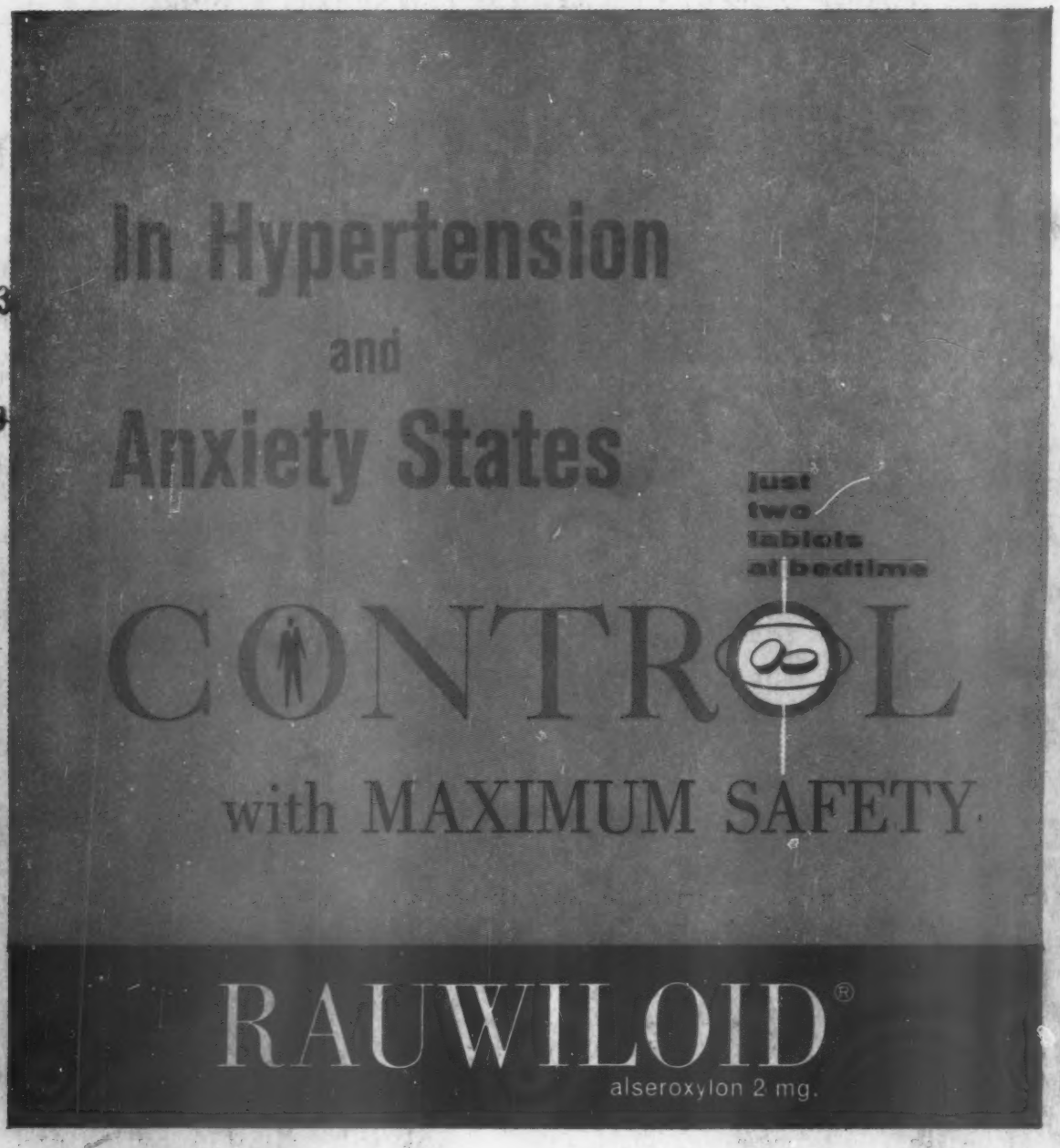
Indication: For the management of hyperlipemia associated with atherosclerosis, especially in the postcoronary patient.

Dosage: After each meal, hold one tablet under the tongue until dissolved.

Supplied: 'Clarin' is supplied in bottles of 50 pink, sublingual tablets, each containing 1500 I.U. of heparin potassium.

*Registered trade mark. Patent applied for.

Thos. Leeming & Co., Inc.
New York 17, N. Y.



In Hypertension
Simplicity of control based on negligible incidence of serious side actions, simplicity of dosage, and applicability to a wide range of patients.

In Anxiety States
Rauwiloid is outstanding for its calming, nonsoporific sedation in anxiety states...with or without hypertension.

Compatible with other antihypertensive medications. Potentiates therapeutic action of more potent agents and permits their use in reduced and better tolerated dosage.

When more potent hypotensive action is needed, prescribe one of these convenient single-tablet combinations

Rauwiloid® + Veriloid®
alseroxylon 1 mg. and alkavervir 3 mg.

or

Rauwiloid® + Hexamethonium
alseroxylon 1 mg. and hexamethonium chloride dihydrate 250 mg.

Patients with severe hypertension often can be maintained on Rauwiloid alone after desired blood pressure levels are reached with combination medication.

Riker Northridge, California